INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

**Stressor Effects on Immune and Endocrine Parameters in Normal and
Depressed Individuals: Influence of Behavioral Characteristics**

**A thesis presented to the Faculty of Graduate Studies and Research of
Carleton University in partial fulfillment for the degree of Doctor of
Philosophy in Psychology with Neuroscience Specialization**

**Marilee D. Zaharia
Department of Psychology
Carleton University**

December, 1998

© Copyright

1998, Marilee Zaharia

**National Library
of Canada**

**Acquisitions and
Bibliographic Services**

**395 Wellington Street
Ottawa ON K1A 0N4
Canada**

**Bibliothèque nationale
du Canada**

**Acquisitions et
services bibliographiques**

**395, rue Wellington
Ottawa ON K1A 0N4
Canada**

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-37083-6

The undersigned recommend to the
Faculty of Graduate Studies and Research
Acceptance of the thesis:

**“Stressor Effects on Immune and Endocrine Parameters in Normal and
Depressed Individuals: Influence of Behavioural Characteristics”**

submitted by

Marilee D. Zaharia

in Partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Chair

External Examiner

Thesis Supervisor

Carleton University
December, 1998

Abstract

There is considerable evidence suggesting that stressful events alter immune, endocrine and neurotransmitter activity, and may promote the development or exacerbate depressive illness. The present investigation was conducted to determine whether stressors influence several aspects of immune and neuroendocrine functioning, and to ascertain whether any such effects are related to pre-existing depressive symptomatology. Accordingly, nondepressed Carleton University Introductory Psychology students were evaluated to determine whether alterations of endocrine and functional immune activity would be associated with exposure to (a) laboratory challenges and/or (b) the anticipation of an academic examination. In addition, we assessed whether the biological responses to these stimuli would be influenced by subjects' behavioral profiles (e.g., depressive symptomatology, stressor history, use of coping strategies, as well as Quality of Life indices). Furthermore, it was determined whether dysthymic disorder, like major depression, is associated with immune changes, and whether these immune alterations would vary with the specific characteristics of the illness (i.e., chronicity and/or the neurovegetative features).

Carleton University Introductory Psychology students exposed to either a simple (i.e., an arithmetic challenge or an clinical interview concerning their daily stressors/negative life events) or a complex (arithmetic plus the preparation and delivery of a speech of either a neutral or emotionally-laden topic) laboratory challenge did not display significant alterations of endocrine or immune activity. However, subjects exposed to a semi-structured clinical interview exhibited elevated plasma NE prior to and immediately following the interview. In contrast to the laboratory challenges, subjects tested either 30-60 minutes or 24 hours prior to an academic examination showed marked increases of lymphocyte proliferation stimulated by concavalin A (Con A), and to a lesser extent, phytohemagglutinin (PHA). Subjects tested one hour, but not 24 hours, prior to the examination also showed elevations of plasma adrenocorticotropin hormone (ACTH),

prolactin, norepinephrine (NE) and epinephrine (Epi) concentrations. Interestingly, marked reductions of lymphocyte proliferation, as well as concomitant increases of neutrophil activity, were exhibited among a subset of subjects tested 10-14 days after the cessation of the entire examination period. Certain behavioral variables, including stressor history and the use of coping strategies predicted the patterns of hormonal and immune alterations prior to the examination, particularly when examined within the context of pre-existing depressive symptomatology. Furthermore, it seemed that levels of Life Satisfaction, as well as Mastery, were positively related to the magnitude of the changes of cell proliferative activity associated with the examination challenge.

Prior to treatment, both typical and atypical dysthymic patients showed marked decreases of lymphocyte proliferation relative to individuals with major depression and controls. In addition, typical, but not atypical, major depressives exhibited reduced cell proliferation relative to the control subjects. Overall, the reductions of immune activity exhibited by the dysthymic groups were not readily modifiable by treatment with selective serotonergic reuptake inhibitors (SSRIs). Yet, notable trends of immune activity were demonstrated among the individuals who responded to SSRI treatment. Major depressives showed a decline of lymphocyte proliferation following successful pharmacotherapy, whereas dysthymic subjects exhibited a 35 percent increase of these immune measures. Like major depression, it seems that dysthymic disorder may be associated with considerable changes of functional immune activity, likely owing to the chronic nature of the illness. Moreover, further normalization of *in vitro* measures of lymphocyte proliferation among dysthymic patients following successful pharmacotherapy may require treatment over a more extended period (e.g., 6 months).

The present findings are discussed in the context of immunological and neuroendocrine correlates of subclinical levels of depressive symptomatology, as well as the influence of stressful events on these processes.

Acknowledgments

I would like to thank Dr. Hymie Anisman very much for his encouragement, expertise, and the support he has always given me during my studies, especially during the "crunch times". Much appreciation is extended to Dr. Jerzy Kulczycki for his excellent teaching and technical assistance (I now have coffee-making skills, too).

Warmest thanks goes to my mother and sister who gave me emotional support throughout my academic career and, everyone at the ROH and our laboratory, who helped me in many ways - Jenna, A.V. Ravindran, James, Jamie, Karen B., Karen L, Nathalie, Nisha, Shawn, Sandra, Sue and Yael. Last but not least, I wish to thank Wayne for all of his love and support throughout my studies.

This research was supported by a grant from PMAC-MRC (Pfizer Canada Inc. and the Medical Research Council, Canada).

In Loving Memory of

Daniel Alexander Zaharia

August 5/15 - March 23/97

Table of Contents

Title Page	i
Acceptance Sheet	ii
Abstract	iii
Acknowledgments	v
Dedication	vi
Table of Contents	vii
List of Tables	ix
List of Figures	xvii
Introduction	1
i) Overview	2
ii) Stressor Effects on HPA Activity	5
iii) Stressor Effects on Immunological Functioning	8
iv Depression: Stress and Endocrine Correlates	21
v) Enumerative and Functional Immune Alterations Associated with Depressive Illness	24
vi) Rationale for the Present Investigation	28
 I. Experiment 1A: Influence of Self-Reported Life Events & Daily Hassles on Basal Endocrine & Immune Activity	 29
 Experiment 1B: Influence of Laboratory Stress on Immune & Neuroendocrine Parameters Among First Year University Students	 55

II. Experiment 2A: Influence of Depressive Symptomatology plus Complex Laboratory Stress on Endocrine & Immune Activity Among	60
Experiment 2B: Influence of Examination Stress on Immune & Neuroendocrine Activity Among University Students	65
III. Experiment 3: Influence of Anticipation of Exams Session on Immune & Neuroendocrine Activity Among University Students: Time Course Assessments	79
IV. Experiment 4: Influence of Depressive Subtype on Immune & Neuroendocrine Activity Prior to & Following SSRI Treatment	94
General Discussion	105
Summary	139
References	142
Tables	172
Figures & Figure Captions	230
Appendices	275

List of Tables

- Table 1. Summary of Stressor-Induced Alterations of Enumerative Measures Among Nondepressed Populations.
- Table 2. Summary of Stressor-Induced Alterations of Functional Immune Measures Among Nondepressed Populations.
- Table 3. Summary of Enumerative Immune Measure Alterations Associated with Depressive Illness.
- Table 4. Summary of Functional Immune Measure Alterations Associated with Depressive Illness.
- Table 5. Cytokine Alterations Associated with Stressors & Depressive Illness.
- Table 6. Mean Basal Plasma Norepinephrine, Epinephrine, ACTH, Cortisol & Prolactin for All Subjects Participating in Experiments 1, 2 & 3.
- Table 7. Mean Basal $[H]^3$ Con A & PHA-Stimulated Cell Proliferation (c.p.m.) as well as PMA-Stimulated Macrophage & Neutrophil Activity (r.l.u.) for All Subjects Participating in Experiments 1, 2 & 3.
- Table 8. Mean Scores for the Beck Depression Inventory, Perceived Stress Scale, UCLA Loneliness Scale, Life Events Scale, Daily Hassles & Uplifts Scale & the Coping Strategies Scale for All Subjects Participating in Experiments 1, 2 & 3.
- Table 9A. Mean Scores for the Beck Depression Inventory, Perceived Stress Scale, UCLA Loneliness Scale, Life Events Scale, Daily Hassles & Uplifts Scale & the Coping Strategies Scale for Male Subjects with Low, Moderate or High Beck Depression Inventory Classifications.
- Table 9B. Mean Scores for the Beck Depression Inventory, Perceived Stress Scale, UCLA Loneliness Scale, Life Events Scale, Daily Hassles & Uplifts Scale & the Coping Strategies Scale for Female Subjects with Low, Moderate or High Beck Depression Inventory Classifications.

- Table 10A. Mean Battelle Quality of Life Subscale Scores of Male Subjects with Low, Moderate or High Beck Depression Inventory Classifications.
- Table 10B. Mean Battelle Quality of Life Subscale Scores of Female Subjects with Low, Moderate or High Beck Depression Inventory Classifications.
- Table 11. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Basal Plasma ACTH Concentrations.
- Table 12. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Emotional Expression Plus Social Support Seeking Scores & Emotional Containment Plus Passivity Scores on Basal Plasma Cortisol Concentrations.
- Table 13. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Emotional Containment and Passivity Scores on Basal Plasma Prolactin Concentrations.
- Table 14A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Social Interaction & Life Satisfaction Scores on Basal Plasma Cortisol Concentrations.
- Table 14B. Multiple Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Social Interaction Scores & Life Satisfaction Scores on Basal Plasma Cortisol Concentrations.
- Table 14C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Social Interaction & Life Satisfaction Scores on Basal Plasma Prolactin Concentrations.
- Table 15A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Basal Plasma Cortisol Levels on Basal 2.0 ug Con A-Stimulated Lymphocyte Proliferation.

- Table 15B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Basal Plasma Cortisol Levels on Basal 5.0 ug Con A-Stimulated Lymphocyte Proliferation.
- Table 16A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Basal Plasma Cortisol Levels on Basal 1.25 ug PHA-Stimulated Lymphocyte Proliferation.
- Table 16B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Basal Plasma Cortisol Levels on Basal 2.5 ug PHA-Stimulated Lymphocyte Proliferation.
- Table 17A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Emotional Expression Plus Social Support Seeking Scores on Basal 1.0 ug Con A-Stimulated Lymphocyte Proliferation.
- Table 17B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Emotional Expression Plus Social Support Seeking & Individual Coping Plus Cognitive Restructuring Scores on Basal 2.0 ug Con A-Stimulated Lymphocyte Proliferation.
- Table 17C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Emotional Expression Plus Social Support Seeking Scores on Basal 5.0 ug Con A-Stimulated Lymphocyte Proliferation.
- Table 18A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Plasma Cortisol & Individual Coping Plus Cognitive Restructuring Scores on Basal 2.0 ug Con A-Stimulated Lymphocyte Proliferation.
- Table 18B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Plasma Cortisol & Individual Coping Plus Cognitive Restructuring Scores on Basal 5.0 ug Con A-Stimulated Lymphocyte Proliferation.

- Table 19A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Life Satisfaction Scores on Basal 1.0 ug Con A-Stimulated Lymphocyte Proliferation.
- Table 19B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Life Satisfaction Scores on Basal 2.0 ug Con A-Stimulated Lymphocyte Proliferation.
- Table 19C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Life Satisfaction Scores on Basal 5.0 ug Con A-Stimulated Lymphocyte Proliferation.
- Table 20A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on Basal 0.625 PHA-Stimulated Lymphocyte Proliferation.
- Table 20B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on Basal 1.25 ug PHA-Stimulated Lymphocyte Proliferation.
- Table 20C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on Basal 2.5 ug PHA-Stimulated Lymphocyte Proliferation.
- Table 21. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on Basal Neutrophil Activity.
- Table 22A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & *Absolute* Change of Plasma Prolactin Levels on *Absolute* Change of 1.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.
- Table 22B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & *Absolute* Change of Plasma Prolactin Levels on

Absolute Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

Table 22C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & *Absolute* Change of Plasma Prolactin Levels on *Absolute* Change of 5.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

Table 23A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Percentage Change of Plasma Cortisol Concentrations Immediately Prior to an Introductory Psychology Examination.

Table 23B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Percentage Change of Plasma Prolactin Concentrations Immediately Prior to an Introductory Psychology Examination.

Table 24. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Emotional Expression Plus Social Support Seeking Scores on Percentage Change of Plasma Prolactin Levels Immediately Prior to an Introductory Psychology Examination.

Table 25. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Percentage Change of Plasma Epinephrine Levels Immediately Prior to an Introductory Psychology Examination.

Table 26. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Perceived Stress on Percentage Change of Plasma Norepinephrine Levels Immediately Prior to an Introductory Psychology Examination.

- Table 27A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 1.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination
- Table 27B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.
- Table 27C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 5.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination .
- Table 28. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Satisfaction Scores on the Absolute Change of Plasma Epinephrine Levels Immediately Prior to an Introductory Psychology Examination.
- Table 29. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on *Absolute* Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation
- Table 30A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Percentage Change of Plasma Prolactin Levels on Percentage Change of 1.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.
- Table 30B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Percentage Change of Plasma Prolactin Levels on Percentage Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

- Table 30C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Percentage Change of Plasma Prolactin Levels on Percentage Change of 5.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.
- Table 31. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Percentage Change of Plasma Prolactin Levels Immediately Prior to an Introductory Psychology Examination.
- Table 32A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 0.625 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Midterm Examination.
- Table 32B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 1.25 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Midterm Examination.
- Table 32C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 2.50 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Midterm Examination.
- Table 33A. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Emotional Containment Plus Passivity Coping Scores on Percentage Change of 0.625 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Midterm Examination.
- Table 33B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage

Change of 1.25 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Midterm Examination.

Table 33C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Emotional Containment Plus Passivity Coping Scores on Percentage Change of 2.50 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Midterm Examination.

Table 34A. Hierarchical Regression Analysis of the Effects of Beck Depression Inventory (BDI) Scores, Mastery & Life Satisfaction Scores on Percentage Change of 1.0 ug Con A-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Final Examination.

Table 34B. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Mastery & Life Satisfaction Scores on Percentage Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Final Examination.

Table 34C. Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Mastery & Life Satisfaction Scores on Percentage Change of 5.0 ug Con A-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Final Examination.

Table 35. Simple Regression Analyses for the Effect of Mastery on Percentage Changes of 0.625, 1.25 & 2.5 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Final Examination.

List of Figures

- Figure 1.** Mean (+SEM) basal peak PMA-stimulated neutrophil activity (r.l.u.) as a function of gender and Beck Depression Inventory (BDI) classification (Low, Moderate or High).
- Figure 2.** Mean (+SEM) concentrations of plasma ACTH (pg/ml), cortisol (ug/dl), and prolactin (ug/L) as a function of a simple laboratory challenge (control, arithmetic challenge or a clinical interview) over time (min.).
- Figure 3.** Mean (+SEM) plasma norepinephrine (NE) and plasma epinephrine (Epi) concentrations (pg/ml) as a function of a simple laboratory challenge (control, arithmetic challenge or clinical interview) over time (min.).
- Figure 4.** Mean (+SEM) Con A- (1, 2 and 5 ug) and PHA- (.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation as a function of a simple laboratory challenge (control, arithmetic challenge or clinical interview) over time (min.).
- Figure 5.** Mean (+SEM) concentrations of plasma ACTH (pg/ml) and cortisol (ug/dl) as a function of Beck Depression Inventory (BDI) classification (Low or High) and a complex laboratory stressor over time (min.).
- Figure 6.** Mean (+SEM) plasma norepinephrine (NE) and plasma epinephrine (Epi) concentrations (pg/ml) as a function of Beck Depression Inventory (BDI) classification (Low or High) and a complex laboratory challenge over time (min.).
- Figure 7.** Mean (+SEM) Con A- (1, 2 and 5 ug) and PHA- (.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation as a function of a complex laboratory challenge over time (min.).
- Figure 8.** Mean (+SEM) concentrations of plasma ACTH (pg/ml), cortisol (ug/dl), and prolactin (ug/L) at baseline and at 30-60 min. prior to an Introductory Psychology examination.

Figure 9. Mean (+SEM) percent change of concentrations of plasma prolactin (ug/L) 30-60 min. prior to an Introductory Psychology examination as a function of Beck Depression Inventory (BDI) classification (Low, Moderate or High).

Figure 10. Mean (+SEM) concentrations of norepinephrine and epinephrine (pg/ml) at baseline and 30-60 min. prior to an Introductory Psychology examination.

Figure 11. Mean (+SEM) Con A-(1, 2 and 5 ug) and PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation at baseline and 30-60 min. prior to an Introductory Psychology examination.

Figure 12. Mean (+SEM) concentrations of plasma ACTH (pg/ml), cortisol (ug/dl), and prolactin (ug/L) among subjects tested at baseline and 24 hours prior to a midterm examination session.

Figure 13. Mean (+SEM) concentrations of plasma cortisol (ug/dl) among subjects tested at baseline and 24 hours prior to a midterm examination session, as a function of Beck Depression Inventory (BDI) classification.

Figure 14. Mean (+SEM) concentrations of plasma ACTH (pg/ml), cortisol (ug/dl), and prolactin (ug/L) among subjects tested at baseline and 24 hours prior to a final examination session.

Figure 15. Mean (+SEM) Con A-(1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation 24 hours prior to a midterm exam.

Figure 16. Mean (+SEM) Con A-(1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation 24 hours prior to a final exam.

Figure 17. Mean (+SEM) Con A- (1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation 24 hours prior to a final exam and 10-14 days after cessation of the final exam period (n = 10).

Figure 18. Mean (+SEM) peak PMA-stimulated macrophage & neutrophil activity at baseline & 24 hours prior to a midterm exam period.

Figure 19. Mean (+SEM) peak PMA-stimulated macrophage & neutrophil activity at baseline & 24 hours prior to a final exam period.

Figure 20. Mean (+SEM) peak PMA-stimulated macrophage & neutrophil activity at baseline & 24 hours prior to, and 10-14 days after the cessation of a final exam period

Figure 21. Mean (+SEM) Con A-(1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation at baseline among control, typical major depressive, atypical major depressive, typical dysthymic, and atypical dysthymic subjects.

Figure 22. Mean (+SEM) Con A-(1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation at baseline & following 12 weeks of SSRI treatment among dysthymic subjects.

Figure 23. Mean (+SEM) Con A-(1, 2 and 5 ug) stimulated lymphocyte proliferation at baseline & week 12 among dysthymic subjects responding to SSRI treatment.

Stressor Effects on Immune and Endocrine Parameters in Normal and Depressive Subtypes: Influence of Behavioral Characteristics

There is considerable evidence suggesting that stressors alter immune, endocrine and neurotransmitter activity and thus, may come to affect both psychological and physical illnesses (see: Anisman & Zacharko, 1990; Anisman, Zalcman, & Zacharko, 1993; Kiecolt-Glaser & Glaser, 1995; Maier, Watkins, & Fleshner, 1994; Stein, et al., 1991, for reviews). In this respect, aversive events, by virtue of the immune alterations imparted, may increase vulnerability to viral illnesses or exacerbate already existent pathology (Cohen & Williamson, 1991). Of course, it is equally likely that stressors may not influence disease processes, but may simply increase the likelihood of individuals perceiving the symptoms of illness (Cohen & Herbert, 1996).

There have been numerous reports showing that affective state, and particularly, depressive illness, are associated with immune alterations (Herbert & Cohen, 1993; Maes, 1995; Miller, Spencer, McEwen, & Stein, 1993; Ravindran, Griffiths, Merali, & Anisman, 1995a; Ravindran, Griffiths, Merali, & Anisman, 1996a; Ravindran, Griffiths, Zaharia, Merali, & Anisman, 1997; Weisse, 1992). However, it is not clear whether depression or even depressive personality directly affects immune functioning or whether immune alterations are secondary to symptoms of depressive illness (Stein, et al., 1991; Weisse, 1992). While studies of depression and immune functioning have typically been correlational in nature, the tacit assumption has been that the immune alterations are secondary to depressive symptomatology. However, there is also reason to believe that immune alterations may, by virtue of their endocrine and neurochemical sequelae, influence affective illnesses (Maes, 1995; Ravindran, et al., 1995a, Ravindran, et al., 1996a; Stein, et al., 1991; Weisse, 1992). Furthermore, the possibility ought to be entertained that depressive illness is associated with a variety of neurovegetative symptoms (including disturbances of sleep and eating), as well as increased stress perception, any of which may impact on immune activity (Maes, 1995; Ravindran, et al.,

1997). While there have been numerous studies that have related severity of depression to immune disturbances, there have been few studies that assessed the immune disturbances in relation to specific characteristics (symptoms) of depressive illness.

The present investigation was conducted to identify some of the factors that may lend themselves to stressor-induced immune dysregulation. In particular, we examined: a) the neuroendocrine and immune changes associated with laboratory stressors and with a naturalistic stressor (i.e., the anticipation of an academic examination), b) whether, in nondepressed individuals, responses to laboratory stressors are influenced by preexisting depressive symptomatology c) whether depressive illness is associated with functional immune alterations (such as macrophage and neutrophil activity, and mitogen-stimulated cell proliferation), d) whether these immune alterations vary with the specific characteristics of the illness (i.e., presence of typical versus atypical symptoms) and, e) whether functional immune alterations are evident in low grade, chronic depression (dysthymia) as previously reported in acute major depressive disorder.

In the sections that follow, a brief overview is presented of the human literature concerning (a) the relationship between stressful events and variations of hypothalamic-pituitary-adrenal (HPA) axis functioning, (b) the impact of acute and chronic stressors on immune functioning, and, (c) the relationship between such alterations of HPA/immune activity and depressive symptomatology.

Overview

All living organisms are required to maintain homeostasis in the midst of constant external and/or internal challenges. These challenges are met by variations of biological responses involving the central nervous system, as well as several neuroendocrine, cytokine, autonomic and immunological processes. Moreover, there is considerable evidence suggesting multidirectional communication between these systems/processes, which ultimately, serves to facilitate adaptation to these challenges (Anisman, et al.,

1993; Blalock, 1994; Besedovsky, del Rey, Klusman, Furukawa, Ardit, & Kabiersch, 1991; Dunn, 1990).

It has been proposed that stressful events and immunological challenge may influence similar physiological processes, and that immune challenge may be interpreted by the brain as if it were a stressor (Anisman, Zalcman, Shanks, & Zacharko, 1991; Anisman, et al., 1993; Dunn, 1993). In this respect, both stressor exposure and immunological challenge promote HPA and sympathetic nervous system activation and vice versa (Anisman, et al., 1993; Blalock, 1994).

The physiological changes elicited by environmental challenges are thought to be dependent upon the activation of certain stress-regulatory pathways (Herman & Culligan, 1997). In particular, the specific pathway activated is believed to be contingent upon the type and duration of the stressor experienced. For instance, "systemic" stressors (those which involve immediate physiological threat, such as hypoxia), are readily relayed to the paraventricular nucleus of the hypothalamus via visceral efferent pathways, and thus, physiological processes can be initiated immediately (e.g. HPA activation). "Processive" stressors (those which are psychological in nature, do not involve an immediate threat, and which require the processing of complex sensory information) also promote HPA activation (as well as other processes). However, the nature of these stressors requires the contribution of limbic and forebrain structures for better coordination of physiological responses to complex environmental challenges (Herman & Culligan, 1997). Be this as it may, the possibility ought to be entertained that by virtue of the concomitant neuroendocrine and neurotransmitter sequelae, exposure to stressful stimuli or immunological challenge may increase the likelihood of developing or exacerbating affective illness (Duman, Heninger, & Nestler, 1997).

Of course, in determining the impact of stressors on neuronal processes and on affective states, other characteristics of stressors need to be considered. Among other things, the predictability, controllability, and the chronicity of stressors can determine

the physiological response (see Anisman, et al., 1991, review), as can previous stressor history (e.g. Benschop, Brosschot, Godaert, Smet, Geenen, Olff, et al., 1994; Cohen, Line, Manuck, Rabin, Heise, & Kaplan, 1997; Pike, Smith, Hauger, Nicassio, McClintick, Costlow, et al., 1997). Moreover, there are considerable individual differences in reactivity to environmental challenges with respect to immune functioning during basal and stressful conditions (Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991; Marsland, Manuck, Fazzari, Stewart, & Rabin, 1995; Matthews, Caggiula, McAllister, Berga, Owens, Flory, et al., 1995). These differences include variability in specific behavioral repertoires (e.g., perception of stressors, or use of particular coping styles; Laudenslager, Ryan, Drugan, & Hyson, 1983; Goodkin, Blaney, Feaster, Fletcher, Baum, Mantero-Atienza, et al., 1992; Ravindran, Griffiths, Waddell, & Anisman, 1995b) as well as personal characteristics (e.g. presence of depressive or negative affect; Stone, Bovbjerg, Neale, Napoli, Valdimarsdottir, Cox, Hayden, & Gwaltney, 1992).

In studies examining enumerative immune measures, both stress and depressive illness have been shown to alter the relative numbers of circulating immune cell subtypes (Cacioppo, Malarkey, Kiecolt-Glaser, Uchino, Sgoutas-Emch, Sheridan, et al., 1995; Futterman, Kemeny, Shapiro, & Fahey, 1994; Kang, Coe, & McCarthy, 1996; Manuck, et al., 1991; Matthews, et al., 1995; O'Leary, 1990; Ravindran, et al., 1995a; Stein, et al., 1991). While it has been suggested that stressor exposure and/or depression reduces several functional immune measures, such as natural killer cytotoxicity (Irwin, Daniels, Smith, Bloom, & Weiner, 1987; Irwin, et al., 1990b) and mitogen-stimulated T-cell proliferation (Kiecolt-Glaser, Glaser, Shuttleworth, Dyer, Ogrocki, & Speicher, 1987; Kiecolt-Glaser, Malarkey, Cacioppo, & Glaser, 1994), there have been inconsistencies in this respect (e.g., Cacioppo, et al., 1995; Futterman, et al., 1994; Knapp, Levy, Giorgi, Black, Fox, & Heeren, 1992; Irwin, Caldwell, Smith, Brown, Schuckit, & Gillin, 1990a; Maes, 1995; Kang et al., 1996; Kang, Coe, McCarthy, & Ersler, 1997; Whitehouse, Dinges, Orne, Keller, Bates, Bauer, et al., 1996). In fact, it was recently proposed that

depression (melancholic depression, in particular) influences immune activation much like an acute phase reaction (Maes, 1995). However, as will be subsequently described, the nature of neuroendocrine and immune alterations in affective illness is complicated by characteristic symptomatology and the chronicity of the depression.

Stressor Effects on HPA Activity

Of the many physiological effects of stressors, one of the most prominent and often studied is the activation of the hypothalamic-pituitary-adrenal (HPA) axis (e.g. Checkley, 1996; Chrousos & Gold, 1992; Holsboer, 1992; Meaney, Diorio, Francis, Widdowson, LaPlante, Caldji, et al., 1996). Although the emphasis of the present investigation does not directly pertain to HPA functioning, there is reason to believe that HPA hormones may affect immune system functioning, and thus a brief overview of this topic will be provided.

Stressors may indirectly influence immune activity through their effects on neuroendocrine and neurochemical systems (Berkenbosch, Van Oers, del Rey, Tilders, & Besedovsky, 1987). Further, it has been suggested that HPA activation during periods of stress may be necessary to protect the organism from disruptions in homeostasis (Anisman, et al., 1991; Munck, Guyre, & Holbrook, 1984). For instance, glucocorticoids not only contribute to the production and release of energy substrates, but may also be important in regulating the response to immunological challenges (Munck, et al., 1984). Moreover, variations of HPA functioning may influence forebrain amines, and thus, may affect cognitive and emotional processes (de Kloet & Reul, 1987; Dinan, 1994). The release of adrenal glucocorticoids is an essential response to environmental challenges and is predictably reliable and robust. However, despite the fact that this response has frequently been taken as a hallmark of the stress reaction (Meaney, et al., 1996), individual differences can be profound in this respect (Griffiths, et al., 1997; Lupien et al., 1997; Pruessner, Gaab, Hellhammer, Lintz, Schommer, & Kirschbaum, 1997). Moreover, it seems that normal HPA functioning may be disturbed in some types of

affective illnesses (Gold, Licinio, Wong, & Chrousos, 1995; Holsboer, 1995; Nemeroff, 1996).

It is now exceedingly well established that stressors influence various aspects of the HPA axis, including the release of neuropeptides within the paraventricular nucleus of the hypothalamus (PVN), and hormones from the pituitary and the adrenal glands (Dinan, 1994; Dunn, 1995; Sapolsky, Krey, & McEwen, 1986; Tsigos & Chrousos, 1994). The central drive of the HPA axis is orchestrated by corticotropin-releasing hormone (CRH) and corticotropin-releasing hormone/arginine vasopressin (AVP) neurons within the parvocellular portion of the PVN of the hypothalamus (Berkenbosch, et al., 1987; Sapolsky, et al., 1986; Tsigos & Chrousos, 1994; Uehara, Gottschall, Dahl, & Arimura, 1987). Under typical stressor conditions, CRH and AVP are released into the pituitary portal system and, in turn, stimulate adrenocorticotropin hormone (ACTH) release from the anterior lobe of the pituitary. Moreover, there is ample evidence to suggest that CRH and AVP may act synergistically in stimulating pituitary ACTH release (see Dallman, 1993). The release of ACTH then induces cortisol secretion from the cortex of the adrenal glands, which serves to negatively feedback on subsequent CRH synthesis and release via hippocampal glucocorticoid receptors (Antoni, 1986; Meaney, et al., 1996; Munck, et al., 1984; Sapolsky, Armanini, Packan, Sutton, & Plotsky, 1990; Sapolsky, et al., 1986). This negative feedback activity serves to alter body metabolism and suppress several immunological processes to protect the individual from physiological overactivation (de Kloet, 1991).

Of particular interest for the present study is the observation that immune activation is associated with HPA alterations. In fact, it was recently suggested that stress and immune activation have similar physiological outcomes (Berkenbosch, et al., 1987; Dunn, 1993; Sapolsky, Rivier, Yamamoto, Plotsky, & Vale, 1987) that may promote long-lasting neuroendocrine alterations (De Goeij, Jezova, & Tilders, 1992c; Schmidt, Janszen, Woutonlood, & Tilders, 1995; Tilders, Schmidt, & De Goeij, 1993). Indeed,

CRH release from the PVN is stimulated by cytokines (such as interleukin-1; IL-1) that are secreted by activated immune cells (i.e., mainly macrophages) and, pretreatment with an IL-1 receptor antagonist prevents some of the neuroendocrine and central monoamine changes ordinarily elicited by stressors (Shintani, Nakaki, Kanba, Kato, & Asai, 1995).

As well, both stressors and/or immune processes may influence subsequent HPA responses by acting directly on particular brain regions, such as the PVN. Specifically, repeated stressor exposure or immunological challenge, both of which induce IL-1 release, promote a phenotypic shift of CRH-secreting PVN neurons so that they begin to coexpress CRH and AVP in terminals located within the external zone of the median eminence (De Goeij, et al., 1992c; Schmidt, et al., 1995; De Goeij, Kvetnansky, Whitnall, Jezova, Berkenbosch, & Tilders, 1991; Schmidt, et al., 1995). Subsequently, this CRH/AVP coexpression enhances potential ACTH release owing to the synergistic actions of these neuropeptides (De Goeij, et al., 1991). Interestingly, with the progression of time, coexpression of these neuropeptides can be elicited following even a single stressor session or after acute cytokine exposure (Van Dijken, De Goeij, Sutanto, Mos, de Kloet, & Tilders, 1993). Thus, even relatively innocuous events (as opposed to chronic aversive experiences) may permanently alter HPA responsiveness (Van Dijken, Mos, van der Heyden, & Tilders, 1992; Schmidt, et al., 1995). It needs to be underscored that these "events" are not restricted to those commonly considered stressors, but include immunological challenges which provoke cytokine secretion and HPA activation (De Goeij, et al., 1991; De Goeij, Binnekade, & Tilders, 1992a; De Goeij, Dijkstra, & Tilders, 1992b; De Goeij, et al., 1992c; Van Dijken, et al., 1992; Van Dijken, et al., 1993; Schmidt, et al., 1995). Conceivably, these phenotypic changes of PVN neurons promote not only excessive release of ACTH, but may have lasting effects on central norepinephrine (NE) and serotonin (5-HT) activity (McEwen, 1995). As will be described later, the monoamine and neuroendocrine alterations may increase vulnerability to the development of affective illness (Chrousos & Gold, 1992; Dinan, 1994).

Stressor Effects on Immunological Functioning-Overview

As previously discussed, physical and psychological stressors are known to affect immunological functioning in animals and in humans. Studies in humans have revealed that immune activity may be influenced by both acute naturalistic (e.g. academic examinations; Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984; Zaharia, Ravindran, Griffiths, Remington, Merali & Anisman, 1995) and laboratory stressors (e.g., cognitive challenges, induction of mood states; Futterman, et al., 1994; Knapp, et al., 1992). Likewise, profound immune disturbances have been observed following chronic life stressors, such as having to deal with severe illness (Baron, Cutrona, Hicklin, Russell, & Lubaroff, 1990; Evans, Leserman, Perkins, Stern, Murphy, Tamul, et al., 1995), marital discord (Kiecolt-Glaser, Kennedy, Malkoff, Fisher, Speicher, & Glaser, 1988; Kiecolt-Glaser, et al., 1994; Kiecolt-Glaser, Malarkey, Chee, Newton, Cacioppo, Mao, et al., 1993), chronic caregiving (Irwin, Brown, Patterson, Hauger, Mascovich, & Grant, 1992; Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991; Kiecolt-Glaser, et al., 1987) and bereavement (Irwin, et al., 1987). While a number of studies have demonstrated immunosuppressive responses to stressors, other reports are inconsistent with these observations. This lack of agreement, however, may be due to procedural differences related to the timing and/or the nature of the stressor examined (Anisman, et al., 1993; Dorian, Garfinkel, Brown, Shore, Gladman, & Keystone, 1982; Kang, et al., 1996; Kang et al., 1997; Whitehouse, et al., 1996). Furthermore, variability in personality attributes (Adler, 1994; Kamen-Siegel, Rodin, Seligman, & Dwyer, 1991; Scheier, Matthews, Owens, Magovern, Lefebvre, et al., 1989; Smith, 1992), as well as previous stressor (Pike, et al., 1997) or psychosocial history (Cobb & Steptoe, 1996), may influence both HPA and immune responses to stressors. Accordingly, such variables may have profound implications for subsequent development of disease (Cohen, 1988; Cobb & Steptoe, 1996). Thus, it ought to be considered that stressful experiences may enhance or moderate the neurochemical, neuroendocrine and perhaps immunological responses to

subsequently applied stressors (i.e., sensitization effects; Tilders, et al., 1993). In fact, immune alterations may even be subject to modification by classical conditioning processes (Ader & Cohen, 1991; Dyck, Janz, Osachuk, Falk, Labinsky, & Greenberg, 1990; Dyck & Greenberg, 1991). Accordingly, knowledge of an individual's stressor history is important when assessing if stressors will significantly affect immune processes and thus constitute a potential health risk (Benschop, et al., 1994; Cohen, et al., 1997; Lloyd, 1980; Pike, et al., 1997).

Several approaches have been adopted in order to assess the impact of stressors on immune functioning. As already indicated, a wide variety of stressor types have been evaluated, and the impact of most of these challenges has been assessed with respect to different aspects of immunity. Broadly speaking, the effects of stressors have been assessed in regard to enumerative indices of immune activity (largely comprising the measurement of different types of circulating immune cells or antibodies), functional aspects of immunity (e.g., the cytotoxic abilities of different cell subsets, or the ability of cells to proliferate in response to mitogens), as well as their effects on disease processes (i.e., the occurrence of illness following viral infection). In the sections that follow, a general overview of stressor effects in humans on each of these aspects of immunity will be provided.

Stressor-Induced Alterations of Enumerative Immune Parameters

The influence of stressors on enumerative measures of immunity have been examined in several investigations. These enumerative measures, determined by flow cytometric analyses (McCoy, Carey, & Krause, 1990), establish the absolute numbers of various types of white blood cells in a given blood volume, and the percentage of each cell subtype (O'Leary, 1990). The cell subtypes most often studied are neutrophils, monocytes, CD-3 (the number of circulating T-cells), CD4 (T-helper cells), CD-8 (suppressor/cytotoxic cells), CD16/56 or CD57/CD8 (natural killer [NK] cells) and CD19 (B-cells) cells. In addition, there are studies which distinguish between activated and non

activated cells within a subtype (e.g., Maes, Stevens, Peeters, Declerck, Scharpe, Birdts, et al., 1992).

Although enumerative measures may be sensitive to environmental challenges, it is difficult to interpret the functional significance of these cellular alterations (Cohen, 1987; Cohen & Herbert, 1996). For instance, increased circulation of many lymphocyte subsets is not necessarily indicative of immune activation. These changes could be fairly temporary, acting simply to "prepare" the individual for further physiological insults. Moreover, the alterations in relative cell numbers or percentages may simply reflect a redistribution of immune cells to or from lymphoid organs (e.g., spleen, liver, lymph nodes), rather than representing significant cellular destruction or enhancement of cell proliferation (O'Leary, 1990). Yet, the quantification of both absolute cell counts and percentage of each subtype ought to be considered since well orchestrated immunological responses to challenges require both a minimum number, as well as a certain percentage, of each cell subtype (Cohen & Herbert, 1996; O'Leary, 1990). Moreover, changes in cell trafficking (i.e., the movement of certain cell subtypes from organs to circulation or vice versa) may be adaptive responses to stressful stimuli in order for immune cells to be available at peripheral sites where they may be needed (Dhabhar, Miller, McEwen, et al., 1996).

Both laboratory and naturalistic stressors have been shown to influence circulating immune cell numbers (see Table 1; Futterman, et al., 1994; Hoffman-Goetz & Pedersen, 1994; Kang et al., 1996; Matthews, et al., 1995; Zaharia, et al., 1995). With few exceptions (e.g., Sieber, Rodin, Larson, Ortega, & Cummings, 1992), acute laboratory stressors, such as cognitive challenges like arithmetic problem solving or the Stroop color-word test (Matthews, et al., 1995; Zaharia et al., 1995), the induction of emotional states (Futterman, et al., 1994; Knapp, et al., 1992), and even a brief psychiatric interview (Griffiths et al., 1997), were associated with increases in circulating NK cells and in some instances, elevations of T-cell subsets. For instance, a math

challenge or a psychiatric interview increased circulating NK cells and to a lesser extent, CD8 cells (Griffiths, et al., 1997). Complex laboratory challenges, including a combination of either the Stroop Test plus an arithmetic challenge (Manuck, et al., 1991) or the Stroop Test, a public speaking task, and the Star Tracer task induced increases of CD8 cells (Manuck, et al., 1991) NK cells, T and B lymphocytes as well as monocytes (Matthews, et al., 1995). Similarly, the induction of specified mood states within in a laboratory setting has also been associated with increases of NK, CD4, CD8, and polymorphonuclear (PMN) cells (Futterman, et al., 1994; Knapp, et al., 1992). Paralleling the laboratory studies, acute naturalistic stressors, including physical exercise (Hoffman-Goetz & Pedersen, 1994), a first parachute jump (Schedlowski, Jacobs, Stratmann, Richter, Hadicke, Tewes, et al., 1993), and the anticipation of academic examinations (Griffiths, et al., 1997; Kang, et al., 1996; Zaharia, et al., 1995) were generally associated with increases in several lymphocyte subtypes, including CD3, CD4, CD8, CD19, NK cells and the CD4/CD8 cell ratio.

Interestingly, cell subtypes may be differentially sensitive to acute stressors. For example, NK cells, and to a lesser extent, CD8 suppressor/cytotoxic cells, may be the most responsive to stressful stimuli (Bachen, Manuck, Marsland, Cohen, Malkoff, Muldoon, et al., 1992; Brosschot, Benschop, Godaert, Olff, Smet, & Heijnen, 1994; Futterman, et al., 1994; Griffiths, et al., 1997; Naliboff, Benton, Solomon, Morley, Fahey, Bloom, et al., 1991; Naliboff, Solomon, Gilmore, Fahey, Benton, & Pine, 1995; Ravindran, et al, 1996b). Other subsets are less reactive to stressors because their numbers may only be altered by more intense challenges. For instance, Griffiths et al. (1997) found that the extent of such increases were greater with a more severe stressor, such as an academic examination, as opposed to a milder laboratory task involving a psychiatric interview. While the latter stressor affected only NK and CD8 cells, the former, more intense stressor induced elevations of circulating NK, CD3, CD4, CD8, CD19 cells (Griffiths, et al., 1997). Commensurate with these findings, was the

observation that in response to a relatively severe naturalistic stressor (a parachute jump among novices), the absolute number of several cell subsets were elevated, including CD2, CD3, CD8 and NK cells. However, the increase of circulating NK cells was substantially greater (i.e., a 100% increase immediately following the jump) than that of other cell subtypes, again suggesting greater sensitivity of NK cells to stressor severity (Schedlowski, et al., 1993).

Although the effects of laboratory stressors on immune subsets have revealed fairly consistent findings, it is noteworthy that considerable individual variability of these measures is observed. It was suggested that individual differences in stressor history (i.e., recent daily life hassles and/or major life events) may account for some of variability of stressor-induced immune reactivity between subjects (Brosschot, et al., 1994). In particular, individuals who experienced more frequent daily hassles showed a reduction of circulating NK cells following an acute laboratory stressor (namely, attempts to solve and to teach a confederate to complete an insolvable puzzle) (Benschop, et al., 1994; Brosschot, et al., 1994). Thus, it was suggested that the uncontrollable/unpredictable nature of daily life hassles could account for some of the individual variability of subsequent immune responses to acute laboratory challenges (Brosschot, et al., 1994). Conversely, individuals experiencing significant chronic life stress (in the form of major life events), had *greater* elevations of circulating NK cells following an acute math challenge relative to unstressed subjects (Pike, Smith, Hauger, Nicassio, McClintick, Costlow, et al., 1997). Regardless of the directional fluctuation of cell numbers, stressor history may be an important determinant of how subsequent acute (and potentially, chronic) insults affect circulating cell subtypes (NK cells, in particular). However, current understanding is incomplete with respect to the impact of psychosocial factors (e.g., stress perception, emotional reactivity, use of coping styles) and other behavioral or personality variables (e.g., depressive symptomatology, loneliness and/or trait hostility) influence the effects of acute or chronic stressors on immunological processes.

Unfortunately, to date few studies have evaluated the impact of chronic life experiences on enumerative immune parameters. In contrast to acute stressor exposure, chronic stressors have been associated with either no change or a net reduction of some circulating cell subsets. Moreover, such effects appear to be dependent upon the type (physical vs. emotional) and quality (controllable vs. uncontrollable) of the chronic stressor encountered. For instance, Pike et al. (1997), found no differences in basal circulating lymphocyte subsets among men experiencing chronic life stress (i.e., major life events) compared to controls (although, it will be recalled, that these subjects showed a greater change of NK cell numbers upon reexposure to an acute laboratory stressor). As well, caregivers of demented relatives (Kiecolt-Glaser et al., 1991; Reese, Gross, Smalley, & Messer, 1994) or stroke patients (Reese, et al., 1994) did not show changes in circulating immune cell subsets. In contrast, individuals tested following natural disasters (which are severe and uncontrollable) were found to have fewer B, CD8 suppressor/cytotoxic and NK cells, coupled with increased numbers of neutrophils and antibody titers to latent herpes simplex virus (HSV) (Ironson, Wynings, Schneiderman, Baum, Rodriguez, Greenwood, et al., 1997; McKinnon, Weisse, Reynolds, Bowes, & Baum, 1989). Likewise, exposure to chronic emotionally-laden stressors, such as poor marriage quality or notification of a severe illness, were associated with reduced numbers of CD8 cells, CD57/CD8 (NK) cells (Evans, et al., 1995; Kiecolt-Glaser, et al., 1988) and CD4:CD8 ratios (Kiecolt-Glaser, et al., 1988). It is important to underscore that in the aforementioned studies, the time between the adverse event and the blood sampling was not always consistent, and in some investigations, samples were collected at lengthy intervals following the trauma (e.g., Ironson, et al., 1997; McKinnon, et al., 1989). Thus, these investigations may not have detected elevated cell numbers that may have occurred shortly after the trauma due to the protracted nature of the sampling time.

The physiological mechanisms subserving the stressor-induced elevations of circulating immune cells are not known. It was suggested that these immune alterations

could be influenced by neuroendocrine factors (e.g., Futterman, et al., 1994; Ironson, et al., 1997; McKinnon, et al., 1989) and/or catecholamines (Schedlowski, et al., 1993; Schedlowski, Hosch, Obereck, Benschop, Jacobs, Raab, et al., 1996). Interestingly, while the levels of several T-lymphocyte subsets were inversely related to cortisol levels (i.e., circadian rhythms), the percentage of NK cells were directly associated with cortisol concentrations (Kronfol, Nair, Zhang, Hill, & Brown, 1997). However, these samples were collected during non-stressed periods, and such relationships may not necessarily exist during stressful periods (e.g., see Schedlowski, et al., 1993). Indeed, Griffiths et al. (1997) demonstrated that the elevations of circulating NK cells following a psychiatric interview were independent of levels plasma cortisol, ACTH or NE. Nevertheless, following a more severe stressor, such as the anticipation of an academic examination, increases in circulating cell subsets paralleled the elevations of NE, cortisol and ACTH (Griffiths, et al., 1997). It is uncertain, whether this was a causal relationship in the aforementioned study. However, it cannot be ruled out that particular cell subsets can be increased by plasma endocrine concentrations when the stressor is relatively severe.

In addition to the potential effects of ACTH and/or cortisol, changes to lymphocyte subsets may be mediated by stress-induced alterations of circulating catecholamines. During non-stressed periods, levels of plasma NE are negatively correlated to the percentage of circulating NK cells and positively related to CD4 cell numbers as well as the CD4/CD8 ratio (Knudsen, Courtpayen, Kjaersgaard, & Christensen, 1995). On the other hand, following stressor exposure that elicited elevations of plasma epinephrine (Epi) and NE (i.e., an acute laboratory challenge or a parachute jump among novice jumpers), increases of circulating NK cells were observed (Schedlowski, et al., 1993). Moreover, these elevations of NK cell numbers were attenuated by pre-treatment with the β -adrenergic antagonist, propranolol (Benschop, Nieuwenhuis, Tromp, Godaert, Ballieux, & van Dooren, 1994; Benschop, Jacobs, Sommer, Schurmeyer, Raab, Schmidt, et al., 1996).

Interestingly, the pattern of immune cell circulation depends upon the activation of appropriate catecholamine receptors. It was recently suggested that there are two distinct phases of cell mobilization following catecholamine administration. First, there appears to be a quick mobilization of lymphocyte subsets, thought to be mediated by β_2 -adrenergic receptors. This is followed by a second mobilization of circulating granulocytes (i.e., neutrophils) that is mediated by stimulation of α -adrenergic receptors. In turn, a subsequent decrease of circulating lymphocytes is observed. Further, it has been posited that catecholamines predominantly influence NK and granulocytes numbers, while T and B cells are only mildly affected (Benschop, Rodriguezfeverhahn, & Schedlowski, 1996).

In summary, alterations of enumerative immune measures appear to be affected by environmental challenges. Stressor characteristics, including type (e.g., laboratory vs. naturalistic stressors; controllable vs. uncontrollable), severity and chronicity, may affect certain cell subsets. While acute laboratory and naturalistic stressors may provoke elevations of several lymphocyte subsets, the cells that show the greatest sensitivity to stressor severity are NK, and to a lesser extent, CD8 cells. Chronic, less controllable challenges have been associated with either no change or a net reduction of cell subsets, however, methodological differences between investigations have led to conflicting results. Finally, the extent to which endocrine and catecholamine activity is related to basal or stressor-provoked alterations of these enumerative measures needs to be elucidated further.

Stressor-Induced Alterations of Functional Immune Parameters

In addition to the enumerative variations, stressors are known to influence *in vitro* and *in vivo* functional measures of immunity. These include *in vitro* tests of NK cell cytotoxicity (i.e., the effectiveness of NK cells at killing tumour cells) and cell proliferation assays (which determine the strength of T-cell proliferative responses to mitogenic stimulation). *In vivo* tests involve inoculation with a particular virus (e.g.,

rhinoviruses) and then determining whether the subject develops symptoms ordinarily attributable to the virus (e.g., cold, flu symptoms).

Although several studies have examined the influence of various stressors on these functional immune measures, findings have not been consistent across investigations (see Table 2). The inconsistency in the literature likely stems from factors associated with the specific stressors examined, as well as subject characteristics. In particular, laboratory stressors (e.g., cognitive challenges, noise bursts, the induction of mood states and psychiatric interviews) are not necessarily equivalent in severity or emotional meaning for subjects, and therefore, are qualitatively distinct from acute naturalistic types of stressors. Moreover, chronic naturalistic stressors, by virtue of their duration, likely involve some adaptation of immune activity. Nonetheless, considerable interindividual variability exists in the immunological reactivity to various environmental challenges. Thus, the possibility ought to be considered that certain subject characteristics (e.g., stress perception, emotional reactivity, use of coping strategies, and personality variables) could mediate stressor-provoked alterations of immune activity regardless of the characteristics of the stressor examined (e.g., Manuck, et al., 1991; Marsland et al., 1995).

Laboratory Stressors. Studies which have examined the effects of acute cognitive challenges on functional immune parameters have generally revealed either reductions of mitogen-stimulated cell proliferation (Bachen, et al., 1992; Cacioppo, et al., 1995; Caggiula, McAllister, Matthews, Berga, Owens, & Miller, 1995; Manuck, et al., 1991; Matthews, et al., 1995), or no change (Brosschot, Benschop, Godaert, Smet, Olf, Heijnen, et al., 1992). Interestingly, among studies that distinguished subjects on the basis of sympathetic reactivity, only high sympathetic reactors (i.e., those who showed greater challenge-induced NE and Epi elevations) exhibited reduced proliferative responses following the stressor (e.g., see Manuck, et al., 1991).

In yet another stress-like paradigm that has been employed, it was shown that lymphocyte proliferative responses could be differentially influenced by the induction of particular mood states. In particular, Futterman et al. (1994) observed that among actors, enhanced proliferative responses following the induction of positive mood states and reduced proliferative responses were present following negative moods. In contrast to these findings, however, Knapp et al. (1992) observed reduced proliferative responses following negative or positive mood states, suggesting that the alterations of immune activity were related to the arousal associated with the mood, and not the mood state per se. The variability of these data may have been due to differences in overall subject characteristics. While Knapp et al. (1992) studied subjects obtained from a university campus, Futterman et al. (1994) used actors as subjects, who could have been more emotionally expressive and/or reactive to task stimuli relative to a student population. Thus, the differential alterations of immune activity as a function of positive vs. negative mood states in the latter investigation may have been influenced by population characteristics.

The influence of acute laboratory stressors on NK cytotoxicity has been extensively examined, and again, findings are somewhat inconsistent. Moderate increases of this measure have been observed following various laboratory cognitive challenges (Cacioppo, et al., 1995; Caggiula, et al., 1995), but such effects were dependent upon the age (Naliboff, et al., 1991) and the sympathetic reactivity of the subjects (Matthews, et al., 1995). In particular, a mental arithmetic stressor was associated with increased NK activity among younger, (21-41 years) but not older female subjects (Naliboff, et al., 1991). As well, greater elevations of stressor-induced NK cytotoxicity were observed among subjects who showed high sympathetic arousal in response to the challenge (Matthews, et al., 1995; Sgoutas-Emch, Cacioppo, Uchino, Malarkey, Pearl, Kiecolt-Glaser, et al., 1994). Moreover, the induction of either positive or negative mood states was only associated with small increases of NK activity (Futterman, et al., 1994; Knapp,

et al., 1992), while a self-disclosure task provoked marked increases of this measure among hostile individuals (Christensen, et al., 1996).

In contrast to the aforementioned findings, a role-playing task provoked a decline of NK cytotoxicity (Naliboff, et al., 1995). Unfortunately, it is unclear what factors may have led to such an outcome as opposed to the usually observed increase of this immune parameter. Furthermore, it was also reported that while no changes of NK activity were observed among subjects with perceived control over noise burst stress, a decline of this measure was observed among individuals who perceived they had *no* control over their situation (Sieber, et al., 1992). These data again are inconsistent with the previous findings. Nevertheless, they suggest that stressor controllability may be important for modulating the impact of aversive events on some measures of immune functioning. Additionally, individual characteristics that favor either increased stress perception (e.g., high sympathetic reactivity), lack of situational control and inappropriate responses to stressors (including increased hostility) may be related to stress-induced NK responses. Finally, as observed with circulating cell subsets, previous stressor history may also be an important dimension in determining the immunological responses to laboratory stressors (Pike, et al., 1997).

Naturalistic Stressors. Like laboratory stressors, there have been several investigations that have assessed the functional immune alterations associated with naturalistic stressors. For instance, the anticipation of impending academic examinations have been associated with decreases of both NK cytotoxicity (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Kang, et al., 1996; Kiecolt-Glaser, et al., 1984) and cell proliferation (Glaser, Pearson, Bonneau, Esterling, Atkinson, & Kiecolt-Glaser, 1993). Again, however, other studies demonstrated opposite effects, at least with respect to cell proliferation (Kang, et al., 1996, 1997; Whitehouse, et al., 1996). These inconsistencies may be due to different populations being studied (i.e., medical students vs. first year university students and adolescents), time sampling differences (Kang, et al., 1996;

Whitehouse, et al., 1996), as well as variability in subjects' perceived importance (and hence, stressfulness) of the examination. Interestingly, another acute naturalistic stressor, namely, a parachute jump among novices, was associated with marked enhancement of NK cytotoxicity immediately after the jump. However, one hour following the jump, a significant decline of this measure relative to that observed at baseline (Schedlowski, et al., 1993). Although the mechanisms underlying these data were not elucidated, a parallel increase of the absolute numbers of NK cells occurred immediately after the jump, which was then followed by a sharp decline (below baseline values). Plasma NE was found to be positively related to NK activity (as well as all lymphocyte subsets measured) prior to and immediately after and 1 hour following the jump (r 's = + .33-.62). As well, plasma Epi was mildly associated with NK activity (r = +.33) only 1 hour after the jump (Schedlowski, et al., 1993). On the other hand, plasma cortisol, did not correlate with any of the immune measures.

The associations between circulating NE and Epi and the cytotoxic activity of NK cells are consistent with those previously observed with respect to the enumerative immune measures. However, the relationship between stressor-induced plasma hormones and functional immune activity (i.e., NK cytotoxicity as well as cell proliferation) is less clear, since many investigations examining the effects of either acute laboratory or naturalistic stressors on these immune parameters did not assess blood hormones (e.g., Brosschot, et al., 1994; Christensen, et al., 1996; Futterman, et al., 1994; Knapp, et al., 1992; Naliboff, et al., 1995; Whitehouse, et al., 1996). Moreover, studies that did examine both endocrine and functional immune measures either did not assess the relationship(s) between these variables (e.g., Kiecolt-Glaser, Glaser, Cacioppo, MacCallum, Syndersmith, Kim, et al., 1997), or, did not find any significant relationship(s) between them, as was the case with some studies using laboratory stressors (Manuck, et al., 1991; Naliboff, et al., 1991). Therefore, while there is evidence to suggest that peripheral catecholamines may influence functional immune activity

following acute stressor exposure (at least, with respect to NK cytotoxicity), the relationship between various endocrine parameters and functional immune activity during acute stress remains to be determined.

By virtue of their duration, the impact of *chronic* naturalistic stressors on functional immune activity needs to be distinguished from the effects of acute naturalistic challenges. Generally, more chronic experiences have been associated with compromised immune functioning. For instance, reduced cell proliferative responses to mitogens were observed among men with poor marital quality and/or negative marital interactions, as well as among individuals who had recently experienced a marital separation (Kiecolt-Glaser, et al., 1988; Kiecolt-Glaser, et al., 1997; McKinnon, et al., 1989). Caregivers of demented family members also exhibited attenuated cell proliferation, poorer antibody responses to influenza vaccinations as well as lower levels of virally-provoked IL-1 and IL-2 production *in vitro* (Esterling, Kiecolt-Glaser, & Glaser, 1996; Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994; Kiecolt-Glaser, et al., 1991; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996). Interestingly, NK activity was most affected among caregivers who reported less positive and tangible support (Esterling, et al., 1996; Esterling, et al., 1994). Finally, there have been reports indicating that various forms of chronic stress, such as negative life events (Stone et al., 1992), lower social status (Cohen, et al., 1997) or chaotic/rigid family environments (Clover, Abell, Becker, Crawford, & Ramsey, 1989) were associated with greater risk of infection as well as the development of flu symptoms, supporting the contention that chronic stressors may compromise several forms of functional immune activity.

As previously observed with acute stressors, NK cytotoxicity appears to be most responsive to chronic stressors. Indeed, reductions of this measure were demonstrated among caregivers of demented family members (Esterling, et al., 1996; Esterling, et al., 1994; Kiecolt-Glaser, et al., 1991) and among individuals following bereavement (Irwin, et al., 1987). As well, similar effects were found among persons who dealt with the long-

lasting consequences of a natural disaster, such as Hurricane Andrew (Ironson, et al., 1997). It was suggested that the magnitude of the reductions of NK activity were either affected by the psychological attributes of the stressor, or alternatively, were secondary to behavioral alterations associated with the insults (i.e., disturbed sleeping patterns; Esterling, et al., 1996; Esterling, et al., 1994; Ironson, et al., 1997). Indeed, reduced NK activity was due, in part, to the onset of sleep difficulties that arose among individuals living in areas damaged by Hurricane Andrew (Ironson, et al., 1997).

Not all investigations, however, have demonstrated reduced NK activity among individuals dealing with chronic stressors. Following particularly traumatic stressors (and possibly, ruminations about associated events), such as exposure to human remains at an airplane crash site (Delahanty, Dougall, Craig, Jenkins & Baum, 1997) or exposure to SCUD missile attacks (during the Gulf war), elevations of NK cytotoxicity (Delahanty, Dougall, Craig, Jenkins & Baum, 1997), lymphocyte proliferation as well as cell-mediated lympholysis were observed (Weiss, Hirt, Tarcic, Berzon, Ben-Zur, Breznitz, et al., 1996). These effects, which are not characteristic of those observed following many chronic stressors, could have been attributed to the elevated levels of distress or anxiety (and potentially, sympathetic reactivity) associated with the severe nature of these stressors.

Depression: Stress and Endocrine Correlates

Like the immune alterations previously outlined, stressful events have also been associated with a variety of physical and psychological disorders. In this respect, the most often studied has been depressive illness. Indeed, it has been demonstrated, in both retrospective and prospective studies, that depressive illness is associated with high levels of stress perception. This includes not only major life events (Brown, 1993; Kessler, Price, & Wortman, 1985; Monroe & Depue, 1991; Monroe & Simons, 1991), but also day-to-day hassles or minor annoyances (Monroe & Simons, 1991; Ravindran, et al., 1995b; Ravindran, et al., 1996a). In addition, depressive illness is associated with

excessive use of emotion-focused coping strategies (thought to be less effective coping), at the expense of more effective coping methods (such as problem solving or cognitive restructuring). The fact that depressed individuals exhibit these "stress/coping profiles" make them an interesting population to examine with respect to immune alterations (Ravindran, et al., 1995b; Ravindran, et al., 1996a).

The relationship between stressful life events and depressive illness have been extensively assessed. Among other things, stressful life events are positively related to depressive symptomatology (Lloyd, 1980; Paykel & Cooper, 1992; Paykel, Myers, Dienelt, Klerman, Lindenthal, & Pepper, 1969), just as they are associated with HPA activation (Chrousos & Gold, 1992). Moreover, altered HPA activity has been implicated in the development of depressive illness, and potentially, HPA alterations may subserve some of the immune variations associated with the illness (Ravindran, et al., 1997a; de Kloet & Reul, 1987; Dinan, 1994).

It was recently suggested that like chronic stress, depression is associated with an increased central drive of the HPA axis, impaired negative feedback processes associated with HPA activity, and extensive adrenal atrophy (Checkley, 1996). In addition to elevations of 24 hour plasma cortisol levels (Halbreich, Asnis, Shindledecker, Zumoff, & Nathan, 1985; Pfohl, Sherman, Schelchte, & Stone, 1985; Rubin, Russell, Poland, Lesser, Winston, & Blodgett, 1987), a substantial proportion of major depressive patients display abnormal release from dexamethasone suppression of cortisol secretion (DST) (Carroll, 1982; Stokes & Sikes, 1987), as well as abnormalities of ACTH and cortisol in response to a CRH challenge (see reviews in Holsboer, 1995; Gold, et al., 1995; Nemeroff, 1996; Plotsky, Owens, & Nemeroff, 1995). Moreover, relapse of depression appears to occur more readily among patients that do not exhibit normalization of the DST response following successful therapy (Plotsky, et al., 1995). Potentially, these data could have distinct anatomical correlates as some depressed patients display adrenal atrophy and

enlarged pituitary gland volumes (Nemeroff, Krishnan, Reed, et al., 1992; Rubin, Phillips, Sadow, & McCracken, 1995).

There is also evidence to suggest that depression could be associated with the activation and potentially, phenotypic changes of CRH hypothalamic neurons. For instance, depressed patients show elevations of cerebrospinal CRH (Nemeroff, Widerlov, Bissette et al., 1984). Additionally, suicide victims had reduced numbers of frontal cortex CRH receptors (Nemeroff, Owens, Bissette, Andom, & Stanley, 1988), significant increases in the number of CRH-PVN neurons, and showed increased CRH/AVP coexpression in these neurons (Raadsheer, Hoogendijk, Stam, Tilders, & Swaab, 1994). Potentially, such changes in these neurons could be responsible for the abnormalities of HPA activity observed in depressive illness (Raadsheer, et al., 1994; Tilders et al., 1993). Moreover, inasmuch as depressed individuals display increased stress perception as well as the use of coping styles that do not foster either appropriate or effective responses to life stressors (Ravindran, et al., 1996a; Ravindran, et al., 1996b), it is conceivable that phenotypic changes of CRH neurons (which can occur even following exposure to an acute stressor) could be important for either the development or the exacerbation of depressive illness. Moreover, it is possible that following each subsequent stressor exposure (and/or depressive episode), the increased availability of AVP associated with these phenotypic changes could promote more pronounced neuroendocrine and amine changes until the depressive illness would occur in the absence of precipitating stressors (Ravindran, et al., 1997b).

As discussed earlier, variations of immune activity have been primarily observed among major depressives, who are more likely to show abnormalities in HPA activity (e.g., abnormal DSTs). However, other depressive subtypes (e.g., dysthymic disorder) are not associated with these HPA abnormalities. In contrast to major depression, the frequency of abnormal DSTs is very much reduced among dysthymic patients (Howland & Thase, 1991; Ravindran, et al., 1994; Ravindran, et al., 1997b). Moreover, relative to

control subjects, dysthymic disorder was associated with low mean plasma cortisol which, following treatment with serotonin-acting agents (as with circulating NK cells), returned to normal values (Ravindran, et al., 1994). As well, along with observed elevations in serum interleukin-1 (IL-1), major depressives with atypical symptomatology were observed to have elevations in plasma ACTH (Anisman, et al., 1997b). Thus, like the changes of immune activity, HPA alterations are not necessarily observed in all depressive subtypes, and are likely influenced by the characteristic symptomatology, severity and the chronicity of the depressive illness. Moreover, the relationship between the HPA changes (or the lack thereof) and the immune changes observed among these depressive subtypes remains to be elucidated.

Enumerative & Functional Immune Alterations Associated with Depressive Illness

As with normal individuals experiencing profound life events, persons with depressive illness display alterations of several immune parameters (O'Leary, 1990; Weisse, 1992). In this respect, these changes include both enumerative and functional indices of immunity (see Tables 3 and 4). Major depression has been associated with a suppression of various components of the immune response (Calabrese, Kling, & Gold, 1987; Evans, et al., 1988; Herbert & Cohen, 1993; Kiecolt-Glaser & Glaser, 1991; O'Leary, 1990; but see Stein et al., 1991) including a reduction of mitogen-stimulated lymphocyte proliferation (Calabrese, et al., 1987; Cosyns, Maes, Vanderwoude, et al., 1989; Darko, Lucas, & Gillin, 1986; Kronfol & House, 1984; Kronfol, Nair, Goodson, & al, 1989; Kronfol, Sylva, Greden, Dembinsky, Gardner, & Carroll, 1983; Kronfol, Sylva, Greden, & al, 1982; Levy, Fernstrom, Herberman, et al., 1991; Syvalahti, Eskola, Ruuskanen, & Laine, 1985) and cell-mediated immunity (Hickie, Hickie, Lloyd, et al., 1993). One of the most prominent immune changes was reduced NK cell activity (Darko, Wilson, Golshan, & Gillin, 1991; Darko, Gillin, Risch, et al., 1989; Irwin, Smith, & Gillin, 1992; Irwin, Smith, & Gillin, 1987; Irwin, et al., 1990b; Maes, et al., 1992; Mohl, Huang, Bowden, et al., 1987; but see Stein et al., 1982), which was mitigated with

symptom remission (Irwin, et al., 1990b). While these effects were particularly notable among individuals with melancholic depression, it could be argued that any of the behavioral or physiological changes associated with the illness (e.g., altered sleep patterns, changes in food intake, increased energy expenditure, alterations of vegetative functioning, drug use etc.), as well as their altered stress perception, contributed to the observed changes in immune functioning (Irwin, et al., 1992). Yet, it has been reported that at least some of the immune changes associated with depression (e.g., altered lymphocyte proliferation) were independent of age, sleep disturbances, menopausal status, or prior treatment with benzodiazepines (Cosyns, et al., 1989; Hickie, et al., 1993).

While there is considerable data to support the contention that depressive illness is associated with immunosuppression, other data suggest that depression is either not associated with immune changes or is, in fact, associated with immunoenhancement. For instance, it was reported that neither NK cell activity (Miller, Spencer, McEwen, & Stein, 1993; Schleifer, Keller, Bond, Cohen, & Stein, 1989) nor suppression of the lymphocyte response to mitogens (Darko, et al., 1989; Darko, et al., 1991; Schleifer, et al., 1989; Stein et al., 1991) was disturbed in depressed patients. To some extent, this inconsistency between investigations may be related to the severity of illness (Maes, 1995; Weisse, 1992). Indeed, it was reported that reduced NK cytotoxicity was predominant among melancholic patients, but not among patients with less severe forms of the illness (Weisse, 1992).

Contrary to the view that depressive illness leads to immune disturbances, Maes (1995) has argued that the immunosuppression observed among depressed patients may actually be secondary to the release of immune products (e.g., cytokines from an activated immune system). In effect, Maes argued that depressive illness is associated with an acute phase-like response (including the secretion of proinflammatory cytokines), which then come to inhibit further NK cytotoxic functioning (Maes, 1995). In fact, major depression was associated with altered levels of acute phase response proteins as well as

increased numbers of circulating lymphocyte subsets indicative of an activated immune system (Darko, Lucas, Gillin, et al., 1988; Maes, Bosmans, Suy, Vandervorst, Dejonckheere, Minner, et al., 1991a; Maes, 1995; Ravindran, et al., 1995a; Seidel, Arolt, Huntstiger, Rink, Behinsch, & Kirchner, 1996b). Furthermore, it was demonstrated that at least some of these effects (e.g., elevations of cell subsets, including monocytes and NK cells) were normalized by antidepressant pharmacotherapy (Ravindran, et al., 1995a; Seidel, et al., 1996b).

In addition to the differences in immune functioning and the presence of acute phase proteins, severe melancholic depressive illness was accompanied by alterations of cytokine levels and/or production (see Table 5), including enhanced mitogen-stimulated lymphocyte production of IL-1, IL-2, IL-6 and interferon- γ (IFN- γ), as well as increased serum levels of soluble IL-2 and IL-6 receptors (Maes, Bosmans, Meltzer, Scharpe, & Suy, 1993; Maes, Bosmans, & Meltzer, 1995; Maes, et al., 1995; Sluzewska, Rybakowski, Bosmans, Sobieska, Berghmans, Maes, & Wiktorowicz 1996). These alterations are noteworthy, since persons with depressive illness show increased stress perception (Griffiths, et al., 1997; Ravindran, et al., 1995b; Ravindran, et al., 1996b) and, the effects of cytokines, like IL-1, are remarkably similar to those provoked by stressors (Merali, Lacosta, & Anisman, 1997; Zalcman, Green-Johnson, Murray, Nance, Dyck, Anisman, et al., 1994). Moreover, several cytokines (e.g., IL-1, IL-2 and IL-6) are potent stimulators of HPA activity, and profoundly influence central neurotransmitter activity (Hopkins & Rothwell, 1995). Thus, it was recently suggested that cytokines, by virtue of their influence of central and neuroendocrine activity, could promote or exacerbate depressive illness (Anisman, et al., 1997b; Maes, et al., 1993; Maes, 1995). Likewise, there has been increasingly greater acceptance of the notion that immunological challenges, like other stressors, may contribute to the provocation of mood disorders (Duman, Heninger, & Nestler, 1997).

As indicated earlier, the inconsistent nature of the immune changes associated with depression are likely related to the defining characteristics of depressive illness. To be sure, it is generally accepted that immune disturbances are most prominent among individuals with melancholic depression (Evans, Folds, Petitto, Golden, Pedersen, Corrigan, et al., 1992; Herbert & Cohen, 1993; Maes, 1995; Maes, et al., 1992; Weisse, 1992). However, other characteristics, such as chronicity as well the presence of typical (neurovegetative symptoms such as decreased eating and sleeping) vs. atypical symptoms (reversed neurovegetative symptoms, such as increased eating and sleeping, leaden paralysis as well as increased rejection sensitivity) could come to influence the alterations of immune activity associated with the illness. Indeed, data collected in our laboratory has indicated that in addition to the severity of the depression, the chronicity of the illness, as well as the presence of typical vs. atypical symptoms, may be important in determining changes of circulating lymphocyte subsets as well as IL-1 production (Ravindran, et al., 1997a). For instance, while elevations of circulating NK cells were observed in both dysthymic and moderately severe major depressive patients, these effects were less evident among persons with atypical depression (Ravindran, et al., 1995a; Ravindran, et al., 1997a; Ravindran, et al., 1997b). Moreover, the atypical depressive subgroup also showed elevated serum IL-1 concentrations (Anisman, et al., 1997a). Further to this issue, while mitogen-stimulated IL-1 levels were elevated among dysthymic patients, this was not true of major depressive patients. Finally, the magnitude of the IL-1 increase was directly related to the duration of illness and inversely related to age of onset. (Anisman & Merali, 1997; Ravindran, et al., 1997b). Thus, these data indicate that the variability of the immune alterations associated with depression may be related to the defining characteristics of the illness, including neurovegetative features, as well as illness duration.

Rational for the Present Investigation

In view of the relationship between stressors, depressive illness and HPA/immune activity, several factors need to be addressed. Although the impact of acute laboratory and naturalistic stressors has been examined with respect to several HPA and immune parameters, there is little information regarding the influence of psychosocial and individual characteristics (e.g., stress perception, daily hassles/uplifts, the use of coping strategies) in modulating these effects. Finally, while there is extensive research examining alterations of HPA and immune activity engendered by stressors and/or major depressive illness, studies have not examined the aforementioned functional immune measures among depressive subtypes, including dysthymia and major depression with or without atypical features. As well the immune alterations among these depressive subtypes have not been assessed in response to pharmacotherapy.

In an attempt to address these issues, the present investigation will explore the alterations of HPA activity and/or functional immune measures engendered by: a) acute laboratory stressors b) an acute naturalistic stressor (i.e., the anticipation of an academic examination) and c) daily life hassles and/or negative major life events. The modulatory effects of psychosocial variables on these HPA/immune alterations, including perceived stress, depressive symptomatology, and use of coping strategies will be considered. Moreover, we will determine the nature of functional immune alterations (i.e., mitogen-stimulated lymphocyte proliferation and macrophage/neutrophil activity) among patients with different subtypes of depression before pharmacotherapy. Finally, preliminary data will be examined to determine whether functional immune alterations occur following successful antidepressant treatment.

Experiment 1A: Influence of Self-Reported Life Events & Daily Hassles on Basal Endocrine & Immune Activity

Major stressful life events have been associated with HPA and immune alterations as well as the development and exacerbation of physical illness. Indeed, individuals report more symptoms of illness (Stone, Reed, & Neale, 1987) and are more likely to develop cold infections after experiencing negative life events (Cohen & Williamson, 1991; Stone et al., 1992). It is conceivable that in addition to major stressful life events, daily minor hassles will influence basal immune, HPA and/or sympathetic activity, and thus, might come to affect health status. Experiment 1A was conducted to establish whether relationship(s) exist between various indices of life stressors (e.g., major stressful life events and daily minor hassles) and basal functional immune activity (lymphocyte proliferation in response to T-cell mitogens and macrophage/neutrophil activity), HPA activity (plasma cortisol, ACTH and prolactin) and sympathetic activity (plasma norepinephrine (NE) and epinephrine, EPI) among first year Carleton University Psychology students. Given that other trait and/or psychosocial variables (e.g., the presence of depressive symptomatology or loneliness, the level of stress perception and positive uplifts as well as the use of particular coping strategies) may affect subjects' perception of daily life stress, we also assessed how these behavioral characteristics contributed to endocrine/immune responses to daily stressors and/or major life events.

In the present investigation, the sample size ($N = 174$) does not quite render the statistical power to detect significant relationships between numerous behavioral variables and the aforementioned immune and neuroendocrine measures. Therefore, in assessing the impact of daily life hassles and major life events on these biological measures, limited regression analyses were conducted to determine how subjects' stress perception and their use of coping strategies (using composite scales; see below) were associated with basal endocrine and immune parameters. Inasmuch as the experiments outlined in this thesis will be used as pilot studies to future investigations, behavioral data

concerning stress-related variables (e.g., depressive symptomatology, perceived loneliness and quality of life indices etc.) were collected.

Methods

Subjects

A total of 99 male (20.73 ± 1.96 years) and 75 female (19.98 ± 1.73) years) Introductory Psychology students, obtained from the Carleton University subject pool, participated in the study (age range of 17-26 years). Students who signed-up for the study were contacted by telephone. After the investigator described the details of the study, and verbal informed consent was obtained, subjects were briefly screened for the presence of medical conditions. Exclusion criteria included any viral illness within the preceding 2 weeks, as well as any medical condition which could influence HPA or immune activity including severe allergies, multiple drug adverse reactions, hypertension, recurrent dermatitis, as well as any malignant, hematologic, endocrine, pulmonary, cardiovascular, renal hepatic, gastrointestinal or neurological disease. As well, subjects were excluded if they were taking any prescribed physical (e.g., antibiotics) or psychotropic medication (with the exception of birth control medications among female subjects). Following the telephone screening, each subject was assigned an individual appointment. All subjects were asked to refrain from any food or beverage (with the exception of water) for at least 2 hours prior to their appointment. All subjects received academic/experimental credits for their participation.

Procedures

After written informed consent was obtained, a registered nurse inserted a 21 gauge butterfly catheter into the antecubital fossa of the subject's non-dominant arm. The majority of the subjects ($n = 117$) were asked to relax and watch a neutral film on a television screen ("St. Lawrence: Stairway to the Sea", National Film Board of Canada) for the entire laboratory session. At the time of needle insertion and again following a 20 minute rest period, blood was automatically withdrawn using a Dakmed ambulatory

withdrawal pump and collected in an adjacent room. Subjects were constantly monitored by the experimenter and the nurse through the use of a two-way mirror which was located between the testing and monitoring rooms. At each measurement time, approximately 30-35 ml of blood was taken over a 7-10 minute period. A portion of the subjects ($n = 57$; who subsequently participated in Experiment 3), had a single blood sample obtained over a 2 minute period using a 21 gauge butterfly catheter. For all subjects, collection tubes used for the hormonal analyses (i.e., cortisol, ACTH and prolactin, NE and Epi) contained 1% disodium ethylene tetraacetate (EDTA; 10% per volume in deionized H₂O). Heparinized collection tubes were used for the blood required for the immune assays. Blood samples from all subjects were immediately stored on ice until centrifugation procedures began.

For the endocrine analyses, blood samples were centrifuged at 4° C for 15 minutes at 400g. Several aliquots of plasma were extracted, and were subsequently frozen at -70° C. Analyses of the functional immune measures required the use of fresh whole blood, and thus, samples were processed immediately following the collection procedures.

Immediately following the blood collection procedures, all subjects were given a package of questionnaires to be completed at home with 48 hours. These measures included scales assessing major life events, minor life hassles and uplifts, perceived stress, coping strategies, Quality of Life, as well as subject characteristics, including depressive symptomatology and perceived loneliness. Subjects were then thoroughly debriefed.

Assay Procedures

Plasma Cortisol, ACTH & Prolactin: Levels of plasma cortisol, ACTH and prolactin were determined (in duplicate) by means of commercially available competitive radioimmunoassay (RIA) kits (ICN Biomedicals Inc., CA). These assays have been conducted on a regular basis in our laboratory and have been demonstrated to show a high degree of intra- and inter-assay reliability. Interassay coefficients were less than 10% while

intra-assay coefficients were less than 7% for cortisol, ACTH and prolactin. For the cortisol assay, the antiserum shows cross-reactivity of 6.1% with deoxycorticosterone, 0.29% with progesterone, .19% with cortisol, and negligible (< 0.1%) with other steroids, including aldosterone, dihydroprogesterone, testosterone and estradiol. For ACTH, antiserum shows negligible (< 0.1%) cross reactivity with β -endorphin, α - and β -melanotrophic stimulating hormone (α -MSH and β -MSH, respectively), α -Lipotropin or β -Lipotropin. As well, the prolactin antiserum shows less than 1% cross-reactivity for luteinizing hormone, follicle stimulating hormone, thyroid stimulating hormone and growth hormone.

Radioactive counts for the cortisol RIA were measured using a Beckman scintillation beta-counter (Model #LS5000TD) set for liquid phase samples. For the ACTH and prolactin RIAs, radioactive counts for solid phase samples were measured using a Camberra Packard gamma-counter. Data were expressed as ug/dl plasma for cortisol, pg/ml for ACTH, and ug/L for prolactin.

Plasma Norepinephrine and Epinephrine: Norepinephrine (NE) and epinephrine (Epi) concentrations were determined using high performance liquid chromatography (HPLC) with coulometric detection, using a modification of the procedure suggested by Seegal et al (1986). Amine standards were dissolved in standard diluent (100 ug/ml stock solution). At the time of analysis, aliquots were diluted with 5% trichloroacetic acid to 50 ng/ml.

Plasma amines were extracted from samples using 1 ml alumina tubes (Supelclean LC-WCX; Supelco). Alumina tubes were conditioned using 500 ul 0.5 N hydrochloric acid (excess acid was removed with 1 ml deionized water; dH₂O). Samples (500 ul) were diluted 1:1 with dH₂O and were slowly pushed (approximately 250 ul/min.) through alumina tubes. The alumina tubes were washed twice with 1.0 ml dH₂O followed by the addition of the internal standard (3,4-dihydroxybenzylamine [DHBA]; concentration 144 pg in 30 ul dH₂O) and 250 ul of dH₂O added at a slow, dropwise rate. Amines were eluted from alumina tubes by the addition of 250 ul 0.2M perchloric acid and collected in siliconized glass HPLC

vials. Using a Waters M-6000 pump, guard column, radial compression column (5 μ , C₁₈ reverse-phase, 8 mm x 10 cm, Chromatography Sciences Co.) and a three-cell coulometric electrochemical detector (ESA Model 5100A), 50 μ l of the supernatant was passed through the system at a flow rate of 1.5 ml/min. (1400-1600 PSI). The mobile phase consisted of 850 ml dH₂O, 1.3 g/L heptane sulfonic acid, Na salt, 0.1 g EDTA and 7.3 ml thiethylamine. The pH of the mobile phase was adjusted to 2.45 using phosphoric acid and then 60 ml acetonitrile was added. This solution was then made up to 1L by adding dH₂O, filtered using 0.22 μ m filter paper, and then degassed. To determine concentrations of NE and Epi in each sample (per ml of plasma), the area and height of curves of the output signals were determined by a Hewlett-Packard (Model #HP-3390A) plotting integrator. Data were reported in pg/ml.

Immune Measures

Lymphocyte proliferation: Peripheral blood lymphocytes were isolated by layering blood samples 1:1 with Histopaque-1077 (density=1.077; Sigma #H-8889) followed by centrifugation at 400g for 30 minutes. The lymphocyte layer of each sample was removed, suspended in sterile phosphate-buffered saline (PBS) containing penicillin/streptomycin. Lymphocyte suspensions were then washed 3 times at 400g for 20 minutes. Lymphocytes were counted and resuspended at a concentration of 1×10^6 cells/ml. Lymphocytes were cultured in RPMI-1640 media containing 25mM Hepes, glutamine, sodium pyruvate (5×10^{-5} M) and fetal bovine serum (10%/volume; Life Technologies, Montreal) with or without the mitogens concavalin A (Con A; 1, 2 and 5 μ g/ 10^6 cells) and phytohemagglutinin (PHA; 0.625, 1.25 and 2.5 μ g/ 10^6 cells) in sterile 96-well flat-bottom plates. Following 68 hours of incubation (37°C, 5% CO₂), 0.5 μ Ci of tritiated thymidine [H^3] was added to each culture well for 4 hours. At 72 hours of incubation, plates were frozen at -70°C until cell harvesting could be performed. Subsequently, plates were thawed, and cells were harvested onto 102 x 256 mm filter mats (Skatron Filter Mat #11731 for 12-well harvesters) using a Skatron 12-well harvester (Skatron Instruments,

Norway) attached to a vacuum pump (General Electric Model #SKTT33DN16GX). Filter mats for each sample well were individually placed into 7 ml borosillate glass vials containing 2.5 ml scintillation cocktail (stock solution = 1 L scintanalized toluene containing 42g/L PPO and 0.525 g/L PPOP; Fisher Scientific Cat. #T313-4, #D144-100 and #D145, respectively. Working solution was then made by diluting the stock solution 1:9 with scintanalized toluene). After quenching samples for several hours, radioactive counts for each sample were determined. Higher radioactive counts signified greater levels of cell proliferation within a particular sample well. All data were expressed as radioactive counts per minute (c.p.m.).

Chemiluminescence Determination of Neutrophil Activity: Isolation of neutrophils was performed by layering fresh whole blood samples 1:1 with Histopaque-1119 (density = 1.119; Sigma) and then centrifuging samples at 400g for 30 minutes. The neutrophil layer of each sample was removed, suspended in sterile Hank's Balanced Salt Solution (HBSS; Life Technologies). Each sample was washed 3 times at 400g for 20 minutes. Neutrophils were counted and resuspended at a concentration of 2×10^6 cells/ml. Fresh luminol (stock solution concentration 1×10^{-2} M in dimethyl sulphoxide [DMSO]) was diluted in HBSS every 2 days of experimentation to a final concentration of 1×10^{-4} M. As well, on the day of sampling, the PMA (stock solution concentration = 1×10^{-3} M) was diluted with HBSS to a final concentration of 1×10^{-5} M.

Neutrophil chemiluminescence activity was determined by placing 200 ul of sample into a polystyrene test tube followed by the addition of 200 ul luminol and 200 ul PMA. This mixture was vortexed briefly (5 sec.) and then gently placed inside a single sample luminometer (Lumat Model #LB-9501, Berthold). Measurements of light remissions were recorded every minute for a total of 10 minutes or for 1-2 minutes following the peak response. Due to the multiple data points measured, statistical analyses were performed using only the maximum peak response (in remitted light units; r.l.u.).

Chemiluminescence Determination of Macrophage Activity: The phagocytic activity of macrophages was determined using the same chemiluminescence procedures as those described for neutrophils. In the present experiment, macrophage activity was determined for each subject at each sampling period by using 200 μ l of the lymphocyte cell suspensions (concentration: 1×10^6 cells/ml media) used for the cell proliferation assays. As with neutrophils, macrophage activity was defined as the maximum peak response (r.l.u.) following PMA stimulation.

Behavioral Measures:

Following the blood sampling and debriefing, subjects were asked to complete a series of questionnaires rating recent depressive symptoms, perceived stress, stressful life experiences as well as the use of coping strategies. These questionnaires (provided in Appendix A) included the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the UCLA Revised Loneliness Scale (Russell, Peplau, & Cutrona, 1980), the Life Events Scale (Paykel, Prusoff, & Uhlenhuth, 1971), the Daily Hassles and Uplifts Scales (Kanner, Coyne, Schaefer, & Lazarus, 1981), the Perceived Stress Scale (Cohen, Karmarck, & Marmelstein, 1983), the Battelle Quality of Life Scale (Revicki, Turner, Brown, & Martindale, 1992) and the Coping Strategies Scale (Beckham & Adams, 1984). As described below, the use of these scales allowed a comprehensive assessment of subjects' stressor/coping profiles within the context of levels of reported depressive symptomatology.

Two scales which are associated with mood states are the Beck Depression Inventory (BDI) and the UCLA Loneliness Scale. The BDI is a 13-item self-report measure that has been used to assess the level of depressive symptomatology in normal, major depressive and dysthymic populations (e.g., see Beck & Beck, 1972; Ravindran, et al., 1996b; Ravindran, et al., 1995b). The first 7 items examine the affective component of depression (e.g., feelings of sadness, guilt, self-hatred), whereas the last 7 items assess somatic symptoms (e.g., fatigue, increased effort to complete tasks) (Beck & Beck, 1972;

Beck, et al., 1961). In the present investigation, the BDI was not used as a clinical indicator of depression. However, because the BDI has been reported to be significantly correlated with several standard clinical depression rating measures in nondepressed, major depressive (see Beck & Beck, 1972) and dysthymic populations (Ravindran, Griffiths, Merali & Anisman, 1998, unpublished), it was used as a screening tool for the university students.

In addition to the BDI, the UCLA Revised Loneliness Scale, also a 13-item self-report measure, was used to assess individuals' perceptions of social inclusion/integration, social support, and loneliness (Russell, et al., 1980).

Among the scales examining life stress, the Life Events Scale is a checklist of common negative major life stressors (e.g., death of loved one, moving away to a new city, major/minor financial problems etc.) encountered in the last 6 and 12 months. Both the frequency and intensity of major life events are measured. Moreover, each item (event) was rated for intensity using a large sample and, ratings were averaged to produce standardized intensity scores for each event (e.g., death of a spouse is rated a more intense life event than hospitalization for an severe illness) (Paykel, et al., 1971). This scale has been shown to be useful for assessing stressful life events in both normal and depressive populations (e.g., see Paykel et al., 1971; Ravindran, et al., 1996a; Ravindran, et al., 1995b).

A second scale which measures minor life stressors and positive events is the Daily Hassles and Uplifts Scales (Kanner, et al., 1981). This scale has a checklist format where subjects indicate which minor life stressor(s) and uplift(s) they have experienced within the last month. Subject are then required to rate each hassle and uplift for its severity/intensity on a scale of 1-3 (see Appendix A). Both daily life hassles and uplifts are measured in terms of frequency (number of hassles and uplifts indicated) as well as severity (in the case of hassles) or intensity (uplifts). Additionally, the relative number of hassles compared to uplifts (i.e., the total number of hassles minus the total number of

uplifts) as well as the relative hassle severity to uplift intensity (i.e., the total hassle severity minus the total uplift intensity) can be determined. Indeed, while some subjects may report a high frequency or severity of daily life hassles, these may be offset by the number and intensity of daily uplifts.

Although some subjects may not report major life stressors or significant levels of minor daily hassles, they may perceive their current life situation very stressful. Therefore, the present investigation also included the 14-item Perceived Stress Scale which determines the degree of which an individual perceives their life situation as unpredictable, uncontrollable or overloading. This measure has been reported to be reliable in three samples, coefficient alphas = .84, .85 and .86, respectively (Cohen, et al., 1983). Moreover, its retest correlation was demonstrated to be .85 (Cohen, et al., 1983). For the present investigation, this measure was particularly important in assessing the influence of life stress on baseline immune and endocrine measures as well as the association between the level of perceived stress and depressive symptomatology in a nondepressed university student population. As mentioned previously, individuals with clinical depression do show significantly higher perceived stress scores than do normal nondepressed subjects (Ravindran, et al., 1995b, 1996a). Thus, it was conceivable that students who might report relatively significant levels of depressive symptoms might likewise exhibit elevated stress perception compared those with minimal or no depressive symptomatology.

The examination of stress perception and/or stressful-provoking events need to be considered in conjunction with the coping styles used. After all, stressful experiences in the context of adequate or appropriate coping may have few adverse effects, but even limited stress in the face of inadequate coping may have a detrimental outcome (Lazarus, 1993). Thus, we used the Coping Strategies Scale to measure the coping profiles of our participants (Beckham & Adams, 1984). This scale gives an extensive profile of coping behaviors subjects have used in the preceding two weeks. The individual coping

subscales within this questionnaire include 1) Blame, 2) Emotional Expression, 3) Emotional Containment, 4) Social Support 5) Religious Support, 6) Philosophical/Cognitive Restructuring, 7) General Activity (i.e., distracter activities), 8) Avoidance/Denial, 9) Problem-Solving and, 10) Passivity. This coping scale also contains 3 composite subscales which assess 1) Emotional Expression plus Social Support Seeking, 2) Emotional Containment plus Passivity and, 3) Individual Coping plus Cognitive Restructuring. Some of these coping behaviors are more oriented to emotion-focused coping whereas others are forms of problem-solving approaches to coping (Beckham & Adams, 1984).

Finally, the impact of stressful life events and minor annoyances may be influenced by overall health, social, and occupational functioning as well as life satisfaction. Thus, the final behavioral measure included in the present report was the Battelle Quality of Life Scale (Revicki, et al., 1992). This scale has been reported to be reliable (intraclass correlation coefficients 0.74-.97), and measures 8 aspects of quality of life that are moderately correlated to clinical measures of depression (e.g., Montgomery Asberg Depression Rating Scale; r 's = +.30 to +.62). The Quality of Life subscales include: 1) Health Perception, 2) Energy, 3) Cognitive Function, 4) Alertness, 5) Home Management and, 6) Work Behavior (designed to determine a sickness impact profile), 7) Social Interaction, and finally, 8) Life Satisfaction. For the present investigation, we did not analyze Home Management or Work Behavior as these subscales were not applicable to our student population (however, these subscales were measured so that the structure of the entire scale was not altered).

The combination of the aforementioned behavioral measures allowed the detailed examination of individuals' perceived stress, major and minor stressors recently experienced, quality of life, feelings of isolation or loneliness and/or presence of depressive symptomatology. Moreover, as will be summarized in later experiments, the

inclusion of these scales allowed us to assess behavioral indices which might account for individual variability of stressor-provoked endocrine and/or immune activity.

Statistical Analyses

Several experiments were conducted to assess the relationship between stressful events and various neuroendocrine and immune parameters. As the baseline data from each of these experiments represented otherwise untreated subjects, the baseline data from the initial 3 experiments were pooled and used to perform a series of hierarchical regression analyses to establish a) whether relationship(s) exist between stressor perception (i.e., major stressful life events and/or daily minor hassles) and various baseline physiological measures (including basal HPA, sympathetic and functional immune activity) and, b) whether these associations would be modified by either subjects' depressive affect and/or the use of particular coping strategies (e.g., the use of Emotional Expression plus Social Support Seeking and/or Emotional Containment plus Passivity vs. Individual Coping and Cognitive Restructuring coping strategies). A substantial number of behavioral, neuroendocrine and immune variables were assessed. Therefore, to maximize statistical power, and to prevent the number of Type I errors that could be associated with conducting multiple statistical tests, hierarchical regression analyses were limited to using the endocrine and immune variables as criterion measures. Moreover, only major life events (past 12 months), daily life hassles and the composite coping subscales of the Coping Strategies Scale (i.e., Emotional Expression plus Social Support Seeking, Emotional Containment plus Passivity, and Individual Coping plus Cognitive Restructuring) were used as predictor variables.

In addition to predicting endocrine and immune activity from major life events, minor daily annoyances/uplifts and coping strategies used, other behavioral data concerning stress perception, perceived loneliness and Quality of Life indices were obtained from all subjects. These factors have been demonstrated to vary among clinically depressed populations (e.g., see Ravindran et al., 1998a; Ravindran et al., 1995a; 1995b; Anisman et al., 1998). As such, it was of interest to us to determine whether these behavioral indices

varied according to *subclinical* levels of depressive symptomatology. Thus, participants were classified according to their total BDI score as "Low" (total BDI scores = 0-3), "Moderate" (4-8) or "High" (9 or greater). Since Beck & Beck (1972) reported that an average total BDI score of 9.37 was found among persons with mild *clinical* depression, a score of 9 or greater was used to classify the "High" group within the present experiment. Using gender and BDI classification as between-group variables, a series of 2 (Gender) x 3 (BDI classification) analyses of variance were performed, using the aforementioned stress-related variables as dependent measures. For these analyses, we also used Bonferroni corrections to achieve more conservative α levels and prevent Type I errors.

Results and Discussion

Descriptive Statistics of Basal Endocrine and Immune Measures

Table 6 shows the mean (+SEM) baseline concentrations of plasma norepinephrine (NE) and epinephrine (Epi) (expressed as pg/ml) as well as the plasma concentrations of the HPA hormones ACTH (pg/ml), cortisol (ug/dl) and prolactin (ug/L) for all subjects participating in Experiments 1, 2 and 3.

Insert Table 6 about here

Table 7 illustrates the mean (+SEM) functional immune activity, as measured by Con A and PHA-stimulated lymphocyte proliferation (c.p.m.), for 145 subjects participating in Experiments 1 to 3 (cell proliferation was not conducted in 29 subjects owing to problems with the quality of mitogens, contamination of the cell cultures, or difficulty obtaining blood from the subjects). For the subjects participating in Experiment 3 (n = 58), basal peak macrophage and neutrophil activity (in r.l.u.) are also shown.

Insert Table 7 about here

Descriptive Statistics of Baseline Behavioral Measures

Table 8 shows the mean (+SEM) total scores for the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Perceived Stress Scale (Cohen, Karmarck, & Marmelstein, 1983), and the UCLA Loneliness Scale (Russell, Peplau, & Cutrona, 1980) for all subjects participating in Experiments 1-3. Additionally, Table 8 summarizes the Frequency and Intensity of Major Life Events (Paykel, Prusoff, & Uhlenhuth, 1971), the Frequency and Severity of Daily Hassles and Uplifts (Kanner, Coyne, Schaefer, & Lazarus, 1981), and the use of Emotional Expression plus Social Support Seeking, Emotional Containment plus Passivity, and Individual Coping plus Cognitive Restructuring (Beckham & Adams, 1984).

 Insert Table 8 about here

Inasmuch as a number of the behavioral measures (e.g., the frequency and severity of reported life events and hassles, perceived stress as well as the coping strategies used) varied as a function of levels of depressive symptomatology, as previously reported (Ravindran et al., 1997), BDI scores were entered into regressions equation first to statistically control for the variance shared by these variables (see results of these analyses below). Naturally, it was our interest to assess whether major life events or daily minor hassles were more predictive of basal hormonal and immune activity over and above that which could be uniquely attributed to depressive symptomatology.

A potential complication of using entering subjects' depression scores into the regressions first was that while the BDI scores were highly correlated with some of the biological measures (e.g., PHA-stimulated cell proliferation) in several cases, they were only modestly or even uncorrelated with the criterion measures. Nonetheless, for the purposes of consistency, and the fact that on many occasions (see all Tables 11 and on) the addition of BDI scores into the equation resulted in larger semi-partial standardized

β 's (i.e., BDI scores were acting as a suppressor variable), we did force BDI scores first into all of the subsequent hierarchical regression analyses for all experiments within this thesis.

It was notable that even though subjects were screened for past and present psychiatric history (using the M.I.N.I. psychiatric interview) and were not using any psychotropic medications, 34 out of the 174 subjects (16 men and 18 women) had total BDI scores greater than 9. Twelve of these 34 subjects with High BDI scores had been chosen through mass testing procedures at Carleton University (along with 41 subjects with Low BDI scores) to participate in Experiments 2A and 2B (see methods section below). Therefore, out of 174 total subjects, 22 out of the 121 subjects randomly selected from the sign-up advertisement sheets from the Carleton University Introductory Psychology Subject Pool Board had BDI scores greater than 9 (i.e., approximately 18 percent). It will be recalled that Beck and Beck (1972) suggested that *clinically* depressed individuals classified as having "mild depression" had an average BDI score of 9.2. Thus, it is possible that a notable portion of our sample of Introductory Psychology students could be representative of a mildly depressed (but subclinical) population. Therefore, as we were interested in the unique variance in the basal endocrine and/or immune measures attributable to major life events or daily life hassles, it was appropriate to force BDI scores into the hierarchical regression analyses prior to these other behavioral variables. Then, the proportion of unique variance in each of the endocrine and immune measures accounted for by the stress-related variables was determined (see Tabachnick & Fidell, 1989). Since several hierarchical analyses were performed, the possibility of Type I errors were considered. Thus, all tests of significance of the semi-partial regression coefficients were conducted using a conservative F test recommended by Larzelere & Mulaik (1977), where: $F = R_s^2/k / (1-R_s^2)/(N-k-1)$, and R_s^2 is the proportion of variance in the criterion variable that can be uniquely accounted for a single or specified block of predictors.

Behavioral Measures as a Function of BDI Classification

To demonstrate how these stress-related behavioral indices varied with depressive symptoms, Table 9 illustrates the mean (+SEM) BDI, Perceived Stress and UCLA Loneliness scores, the number and intensity of major life events (in the past 12 months), the number and severity of daily life hassles (vs. daily uplifts) as well as the mean composite Coping Strategies Scale subscale scores among men and women with Low, Moderate, and High BDI classifications.

 Insert Table 9 about here

A series of 3 (Beck Classification) x 2 (Gender) analyses of variance were conducted to assess whether the aforementioned stress-related variables (such as perceived stress, feelings of loneliness, major life events and daily life hassles etc.) varied among men and women within the three BDI subgroups. These analyses indicated that subjects' stress perception and feelings of loneliness varied only as a function of Beck Classification, $F's(2, 154; 2, 160) = 30.39$ and 490.87 , $p's < .0001$. As illustrated in Table 9, relative to individuals with Low Beck scores, those with High Beck scores had significantly greater levels of Perceived Stress and feelings of loneliness.

Additionally, the Beck Classification x Gender analyses of variance demonstrated that the frequency and the intensity of Major Life Events in the past 12 months varied as a function of Gender, $F's(1, 161) = 5.54$ and 3.58 , $p's = .01$ and $.06$, and Beck Classification, $F's(2, 161) = 7.21$ and 8.66 , $p's < .001$, but not as a function of the Beck Classification x Gender interaction, $F's < 1$. In general, males reported having experienced greater frequency and intensity of major life events than did the females. Newman-Keuls multiple comparisons of the main effects ($\alpha = .05$) confirmed that, irrespective of gender, individuals with "High" BDI scores reported greater frequency and intensity of major life events than did subjects with Low BDI scores.

Like Major Life Events, the frequency and severity of Daily Hassles varied as a function of Beck Classification, $F's(2, 161) = 3.64$ and 5.82 , $p's < .05$ (see Table 9). The multiple comparisons confirmed that subjects with High BDI scores reported more frequent hassles and perceived these hassles as more severe relative to individuals with Low BDI scores. Moreover, the differences between the number and severity of these hassles and the number and intensity of daily uplifts (i.e., the number of daily hassles minus the number of uplifts and the severity of these daily hassles minus the intensity of these uplifts, respectively) were also shown to vary as a function of Beck Classification, $F's(2, 161) = 10.11$ and 10.46 , $p's < .01$, respectively. In comparison with the Low Beck subjects, those individuals with either Moderate or High Beck scores showed attenuated differences between hassles and uplifts (both with respect to frequency and severity/intensity). That is, subjects with Moderate and High BDI scores were more likely to show relatively fewer and less intense uplifts relative to the number and severity of hassles. Likewise, differences were noted between Moderate BDI and High BDI subjects with respect to these difference measures. These data are consistent with those observed by Griffiths et al. (1996) and Ravindran et al. (1995b) in that prior to pharmacotherapy, MDD and dysthymic outpatients reported a reduced number and intensity of uplifts relative to the number and severity of daily hassles. The data from the present investigation suggest that, like individuals with MDD or dysthymia, persons with mild (but subclinical) levels of depressive symptomatology also show changes of these stress-related variables. Moreover, these changes appear to be sensitive to the severity of individuals' depressive symptoms.

Although depression is commonly associated with anhedonia, and it has been reported that the perception of uplifting events was reduced in clinically depressed populations (both MDD and dysthymic patients), in the present investigation neither the frequency nor the intensity of daily uplifts *alone* varied as a function of Beck Classification, $F's < 3.00$. As will be discussed later, the lack of group differences with

respect to the frequency and intensity of daily uplifts may be one meaningful way, other than symptom severity, to distinguish between subclinical and clinical forms of depressive symptomatology. Of course, it is possible that the study population in this investigation, which comprised of first year Carleton University Introductory Psychology students, were not representative of clinical or subclinical populations in general, and certainly not that of older subjects that were evaluated in earlier experiments (see Griffiths et al., 1996; Ravindran et al., 1995b).

In addition to the differences of reported major life events and daily hassles, subjects within the 3 Beck classification groups also showed significant variation in the use of coping strategies, such as Emotional Expression plus Social Support Seeking, and Emotional Containment plus Passivity, $F(2, 154) = 20.51$ and 19.50 , $p's < .0001$ (see Table 9). The multiple comparisons confirmed that relative to those with Low BDI scores, subjects with either Moderate or High BDI scores used Emotional Expression and Social Support Seeking more often, but the latter two groups did not differ from one another in the use of these strategies. Moreover, individuals with High BDI scores showed the tendency to use Emotional Containment and Passivity as coping strategies more often than individuals with either Moderate or Low BDI scores. These three groups, however, did not differ with respect to their use of Individual Coping and Cognitive Restructuring, $F < 1$ (see Table 9).

It was notable that the mean BDI score for the men and women in the "High" group (13.0 ± 0.46), was comparable to the mean BDI score observed among a group of dysthymic patients (13.85 ± 0.76) prior to pharmacotherapy (Ravindran et al., 1996a). Additionally, the mean scores concerning the use of Emotional Expression plus Social Support Seeking, Emotional Containment plus Passivity as well as Individual Coping plus Cognitive Restructuring of subjects (men and women) with High BDI scores (means = 46.15 ± 1.69 , 47.32 ± 1.94 , and 48.52 ± 1.81 respectively) were comparable to those reported by Ravindran et al. (1996a) among dysthymic patients (means = 43.61 ± 0.97 ,

45.36 $\pm$ 0.97 and 44.47 $\pm$ 0.96, respectively). These findings, along with those previously discussed with respect to daily hassles and uplifts suggest that individuals with considerable, but subclinical, levels of depressive symptomatology (albeit within the context of a self-report depression measure) may exhibit stressor history and coping profiles similar to those with depression of mild to moderate severity.

Quality of Life Variables as a Function of Beck Classification

It was apparent that several other stress-related variables also varied as a function of the Beck classification (see Table 10). It should be noted that these data were collected and statistical analyses were conducted as preliminary studies to more elaborate studies of the correlates of depressive illness. Yet, recent data collected in our laboratory suggested that Quality of Life may be a particularly meaningful index of residual (and perhaps prodromal) aspects of depression. Accordingly, these data are presented at this juncture.

The General Health, Health Perception, Energy, Concentration (Cognitive functioning), Alertness, Social Interaction and the Life Satisfaction subscale scores of the Battelle Quality of Life Scale all varied as a function of BDI classification, F 's(2, 104) = 15.50, 11.90, 27.93, 27.78, 42.68, 13.57, and 67.67, p 's < .0001. The multiple comparisons confirmed that relative to subjects with Low Beck scores, individuals with BDI scores of 9 or greater showed reduced General Health and Health Perception, as well as reduced Energy and Concentration ratings. Moreover, subjects with either Moderate or High BDI scores showed reduced Alertness, diminished quality of Social Interaction and reduced Life Satisfaction relative to subjects with Low BDI scores (see Table 10).

 Insert Table 10 about here

The Quality of Life ratings as a function of BDI classification are consistent with the group differences reported with respect to life events and/or daily hassles, and provide

a functional quality to these stress/coping profiles. These data also provide the rationale for forcing the BDI scores into the hierarchical regression analyses prior to assessing any potential relationship(s) between basal hormonal and/or immune activity and stress-related behavioral variables. These hierarchical regression analyses, which statistically control for individual differences of depressive symptomatology, are presented below.

Behavioral Correlates of Basal Immune and Endocrine Activity

It is recognized that the prediction of the basal hormonal and immune activity among subjects is exceedingly difficult, due to considerable interindividual variability of both biological and behavioral indices. Accordingly, an attempt was made to reduce the number of stressor history variables that were highly correlated to one another. Interestingly, neither the Frequency nor Intensity of Major Life Events predicted either the number or severity of Daily Hassles, $F's < 1$. These findings suggested that subjects' reported Major Life Events and Daily Hassles were relatively independent of one another. However, the Frequency and Intensity/Severity components within each scale were highly correlated (zero order $r's = +.98$ and $+.90$, $F's(1, 110) = 2954.73$ and 477.25 , $p's < .0001$ for Major Life Events and Daily Life Hassles, respectively). Thus, to reduce the number of hierarchical regressions performed, only the Intensity of Major Life Events and the Severity of Daily Hassles were used as predictors. This is not to say, that among some subjects, the frequency of hassles or major life events are any less important in assessing the relationship between previous stressor history and basal hormonal and immune activity. This procedure was undertaken to simplify the following results and discussion section. In addition, it is conceivable that individuals' perception of the intensity of their life events or hassles may be more sensitive for distinguishing between endocrine/immune profiles among individuals with varying levels of depressive symptomatology.

Plasma ACTH, Cortisol and Prolactin

Hierarchical regression analyses revealed that the Intensity of Major Life Events neither predicted baseline levels of plasma cortisol, ACTH or prolactin after BDI scores were statistically controlled, $F's < 2.00$. Likewise, the Severity of Daily Hassles was not predictive of basal plasma cortisol levels. However, Hassles Severity negatively predicted basal ACTH concentrations ($\beta = -.486$, $sr^2 = .15$), $F(1, 155) = 4.95$ $p < .05$. Individuals who perceived their daily life hassles more severe were more likely to have lower basal concentrations of plasma ACTH (see Table 11). Moreover, the predictive capacity of daily life hassles was not influenced by individuals' use of coping strategies, $F's < 1$. Therefore, levels of basal plasma ACTH among individuals with hassles of greater severity were independent of the types of coping strategies they used.

Insert Table 11 about here

In contrast to daily hassles, the types of coping strategies individuals used significantly predicted basal plasma cortisol concentrations irrespective of baseline BDI scores, $F's(1, 78) = 6.98$ and 5.23 , $p's < .05$, for Emotional Expression plus Social Support Seeking and Emotional Containment plus Passivity, ($\beta's = .34$; $-.29$, $sr^2's = .09$; $.15$), respectively (see Table 12). While the use of Emotional Expression plus Social Support Seeking was associated with greater basal cortisol concentrations, the use of Emotional Containment plus Passivity for coping was associated with reduced plasma cortisol. In addition to plasma cortisol, subjects' use of Emotional Containment plus Passivity positively predicted basal prolactin concentrations ($\beta's = .21$, $sr^2 = .04$), $F(1, 145) = 4.84$, $p < .05$ (see Table 13), although the proportion of unique variance shared between these variables was relatively modest.

 Insert Tables 12 and 13 about here

While the use of particular coping strategies are associated with plasma concentrations of cortisol and prolactin, they only uniquely account for about 4-8 percent of the variance observed in the levels of these hormones. Accordingly, it is not clear whether the use of these particular coping styles are associated with *biologically significant* variations of basal HPA activity. Moreover, these associations are observed irrespective of the severity of daily hassles (as shown earlier with ACTH) or depressive symptomatology. While it seems understandable to consider the use of these coping strategies more "biologically relevant" within the context of an individual's current depressive symptoms and/or stressor history, the present data suggest that subjects' coping profiles can be independently associated with basal endocrine activity, albeit to a moderate degree (see Tables 12 and 13).

As mentioned previously, recent data collected in our laboratory suggested that Quality of Life may be a particularly meaningful index of residual (and perhaps prodromal) aspects of depression (see Table 14). Of particular interest was the finding that two of these Quality of Life indices namely, Social Interaction and Life Satisfaction, were associated with basal concentrations of cortisol and prolactin, but not ACTH ($F < 1$). Indeed, subjects' ratings of Social Interaction and Life Satisfaction predicted levels of plasma cortisol (β 's = $-.28$; $-.32$, sr^2 's = $.05$; $.10$), F 's(1, 84) = 4.61 and 4.44, p 's $< .05$, as well as prolactin (β 's = $-.27$; $-.30$, sr^2 's = $.06$; $.05$), F 's(1, 131) = 8.032 and 6.58, p 's $< .01$ and $.05$, respectively (see Table 14). While Life Satisfaction was negatively associated with both these plasma hormones, diminished Social Interaction was unexpectedly associated with reduced basal plasma cortisol and increased prolactin, respectively. It must be noted that these stress-related variables uniquely accounted for between 5 and 10

percent of the total variance of the plasma cortisol and prolactin among our subjects. Moreover, these Quality of Life variables (i.e., Social Interaction and Life Satisfaction) account for significantly more variance of these hormonal measures if they were considered together, along with level of depressive symptomatology (multiple $R^2 = .10$ and $.10$), F 's (3, 82; 3, 132) = 2.92 and 5.03, p 's < .05 and < .01, for cortisol and prolactin, respectively (see Table 14). At this juncture, the mechanisms underlying these associations are not known, but will be discussed in more detail within the General Discussion.

 Insert Table 14 about here

Plasma Norepinephrine and Epinephrine

Hierarchical regression analyses revealed that neither Intensity of Major Life Events nor the Intensity of Daily Hassles were related to baseline concentrations of plasma norepinephrine (NE) or epinephrine (Epi), F 's < 1. Additionally, subjects' use of coping strategies was not associated with basal NE or Epi, F 's < 1. These findings suggest that once the influence of depressive symptomatology was removed, basal concentrations of these plasma amines were independent of daily minor and major life stressors and the strategies used to deal with these events. Moreover, like plasma ACTH, none of the Quality of Life subscales significantly predicted basal plasma NE or Epi after the effects of subjects' BDI scores were statistically removed, F 's < 2.00.

Mitogen-Stimulated Lymphocyte Proliferation

Although cortisol is often thought to be immunosuppressive, basal plasma cortisol concentrations were consistently positively related to both Con A and PHA-stimulated cell proliferation (β 's = .25; .26, .29; .352; $sr^2 = .06$; .09; .09; .15), F 's(1, 63) = 4.02, 4.58, 5.63 and 9.17, p 's < .05, for 2.0 and 5.0 ug Con A and 1.25 and 2.5 ug PHA, respectively (see Tables 15 and 16). In contrast, there were no other relationships found between the

plasma hormones and the proliferative measures, F 's < 1 . Similarly, basal levels of neutrophil/macrophage phagocytosis were not predicted by the concentrations of plasma hormones, F 's < 1 . These data suggest that, with the exception of plasma cortisol, basal functional immune activity was independent of the hormonal and sympathetic measures. However, as will be illustrated in the ensuing experiments, plasma HPA and sympathetic measures can, in fact, be predictive of the immune activity associated with the anticipation of stressful events.

 Insert Tables 15 and 16 about here

Paralleling the hierarchical regression analyses concerning the baseline hormonal and sympathetic measures (with the exception of plasma cortisol), neither Intensity of Major Life Events nor Severity of Daily Hassles were related to basal levels of Con A and PHA-stimulated lymphocyte proliferation after BDI scores were statistically removed, F 's < 1 .

In contrast to Major Life Events and Daily Hassles, use of Emotional Expression plus Social Support Seeking significantly predicted basal 1.0 and 2.0 ug Con A-stimulated lymphocyte proliferation after the influence of BDI scores were removed (β 's = .206; .231; sr^2 's = .03; .04), F 's(1, 123) = 4.25 and 5.47, p 's $< .05$, respectively. These associations, however, with respect to unique variance of basal immune activity accounted for were relatively modest. Nonetheless, like the hierarchical analyses concerning the behavioral predictors of basal plasma cortisol, subjects with greater use of Emotional Expression plus Social Support Seeking tended to have greater basal Con A-stimulated cell proliferation. Moreover, after the effects of both BDI and Emotional Expression plus Social Support Seeking were removed, the use Individual Coping plus Cognitive Restructuring predicted lower baseline 2.0 ug Con A-stimulated cell lymphocyte proliferation, ($\beta = -.203$; $sr^2 = .08$), $F(1, 122) = 4.57$, $p < .05$ (see Table 17).

Insert Table 17 about here

Summarizing briefly, it appears that coping profiles may be associated with basal functional immune activity, particularly the use of Emotional Expression plus Social Support Seeking and Individual Coping plus Cognitive Restructuring. However, it will be recalled that basal plasma cortisol levels positively predicted Con A, but not PHA-stimulated T-cell proliferation. Moreover, as in the case of the proliferative measures, the use of Emotional Expression plus Social Support Seeking was positively associated with basal cortisol concentrations. It is thus possible that during nonstressful periods, basal cortisol concentrations were greater among individuals who favored Emotional Expression plus Social Support Seeking, and potentially, the shared relationship between this type of coping and the activity of lymphocytes stimulated with Con A was really attributable to its shared variance with cortisol. In fact, when BDI and cortisol concentrations were entered into the regression equations followed by the three composite coping strategies indices, only the use Individual Coping plus Cognitive Restructuring accounted for significantly more unique variance in both 2.0 ug and 5.0 ug Con A-stimulated cell proliferation, (β 's = -.27 and -.26; sr^2 's = .07 and .07, respectively), F 's(1, 57) = 4.50 and 4.44, p 's < .05 (see Table 18). These findings indicate that considering both plasma cortisol concentrations and Individual Coping plus Cognitive Restructuring may be useful in predicting some aspects of functional immune activity during relatively nonstressed conditions.

Insert Table 18 about here

Quality of Life Variables Predict Basal Lymphocyte Proliferation

Paralleling the association with basal plasma prolactin, Life Satisfaction predicted basal levels of Con A-stimulated cell proliferation after the influence of BDI scores were statistically removed ($\beta = -.32; -.29; -.32; sr^2 = .05; .04; .06$), F 's(1, 105) = 5.23, 4.30 and 5.33, $p < .05$ (for the 1.0, 2.0 and 5.0 ug doses of Con A, respectively). Irrespective of degree of depressive symptomatology, subjects who reported greater levels of Life Satisfaction had lower basal levels of Con A-stimulated cell proliferation (see Table 19).

Insert Table 19 about here

In contrast to the Con A-stimulated cell proliferation, Life Satisfaction did not predict the PHA-stimulated mitogenesis after the effects of the BDI scores were removed $F(1, 103) < 2.00$. However, it seemed that Energy was positively related to ($\beta = .24; sr^2 = .06$), 125 ug PHA-stimulated cell proliferation, $F(1, 105) = 4.81$, $p < .05$. Approximately 6 percent of the variability observed among the peak PHA-stimulated cell counts was uniquely attributed to Energy scores (see Table 20). These data suggest that while Life Satisfaction negatively predicted Con A-stimulated cell proliferation, PHA-stimulated mitogenesis tended to be enhanced among those who reported having more physical Energy. Again, however, it should be noted that the unique variance in Con A and PHA-stimulated cell proliferative activity that could be accounted by Life Satisfaction or Energy, respectively, was relatively modest (4-6 percent).

Insert Table 20 about here

Chemiluminescence Determined Macrophage & Neutrophil Activity

Consistent with the lymphocyte proliferation data, neither major life events nor daily life hassles significantly predicted either macrophage or neutrophil phagocytosis,

when the influence of BDI scores were statistically controlled, F 's < 1 . The lack of association between either major life events and daily hassles with macrophage or neutrophil phagocytosis as well as mitogen-stimulated cell proliferation suggests that during relatively nonstressful periods, functional immune activity is independent of these types of stressors.

Interestingly, while neither major life events nor daily minor hassles significantly predicted basal neutrophil activity, this immune measure varied as a function of the Beck Classification (Low, Moderate & High) $\times$ Gender interaction, $F(2, 42) = 3.93$, $p < .05$ (see Figure 1). Newman-Keuls multiple comparisons ($\alpha = .05$) indicated that men with BDI scores greater than 9 displayed enhanced neutrophil activity relative to men with either Low or Moderate BDI scores. Additionally, there was a trend for these men to display greater basal neutrophil activity relative to women with High BDI scores, $p = .08$. These data, however, should be treated with caution, as there were only a total of 43 subjects assessed for basal neutrophil activity. Moreover, the data from women with High BDI scores were quite variable.

 Insert Figure 1 about here

Like the proliferative immune measures, Energy scores positively predicted basal neutrophil activity after the variability attributable subjects' depressive symptomatology was removed ($\beta = .47$; $sr^2 = .24$), $F(1, 21) = 5.03$, $p < .05$ (see Table 21). This finding is also consistent with the PHA-stimulated cell proliferation data, and suggests that at least some of the variability of basal functional immune measures is positively associated with Energy levels. It should be recalled that reported Energy scores were lowest among individuals with High BDI scores (mean = 39.5 ± 3.60 vs. 54.89 ± 3.29 and 69.35 ± 1.88 among subjects with moderate and low BDI scores, respectively). Thus, at least some

aspects of Quality of Life (which vary with levels of depressive symptomatology) are likely associated with basal immune functioning.

 Insert Table 21 about here

Experiment 1B: Influence of Laboratory Stress on Immune & Neuroendocrine Activity Among First Year University Students

The impact of laboratory stress on subsequent immune activity is dependent upon several factors relating to the actual immune measure examined, as well as the specific characteristics of the stressor. While laboratory stressors have been demonstrated to influence particular immune compartments (e.g., circulating cell subtypes), they do not necessarily impact on other aspects of immunity. Moreover, the severity, as well as the type of stressor (i.e., a nonpersonal cognitive challenge vs. an emotionally-laden stressor involving the recollection of personal life experiences) may determine the nature of endocrine and/or immune variations. For instance, it will be recalled that among normal subjects, elevations of circulating NK cells were less evident following a psychiatric interview in comparison to a more severe stressor, such as an academic examination (e.g., see Griffiths, et al., 1997). Moreover, among untreated depressed individuals, elevations of circulating NK cells were observed following a psychiatric interview concerning the positive events in their lives (Griffiths, et al., 1997). Interestingly, increases of NK cell cytotoxicity and reductions of cell proliferation were reported in studies using more complex cognitive challenges (e.g., an arithmetic task followed by the Stroop Test) (Cacioppo et al., 1995; Manuck et al., 1991; Matthews, et al., 1995), whereas immune data were more variable following emotionally-laden laboratory tasks (Futterman, et al., 1994; Knapp, et al., 1992). While there is reason to believe that stressors provoke dynamic variations of immune and endocrine activity, few studies assessed the course of immune changes over time following stressor exposure. Clearly, a systematic

investigation with several sampling times (which includes the appropriate control subjects) is required to determine the dynamics of endocrine and/or immune activity following these distinct types of laboratory stressors.

Accordingly, Experiment 1B examined the time course of potential alterations of immune and/or endocrine activity following two types of simple laboratory stressors (i.e., a mental arithmetic challenge vs. an interview concerning negative life experiences).

Methods

Subjects

A subset of subjects, 19 male (21.69 ± 2.79 years) and 19 female (20.68 ± 1.70 years), from Experiment 1A participated in this study. Exclusion criteria were identical to those in Experiment 1A. Again, all blood sampling was conducted between 0700-1200.

Procedures

Following informed consent being obtained, the registered nurse inserted an i.v. catheter into the subject's non-dominant arm. In addition to being asked to relax and watch the neutral film, subjects were randomly assigned to one of three experimental conditions: 1) Control 2) Math Challenge, and 3) Stress Interview. Following the 20 minute relaxation blood sample, the investigator quietly entered the experimental room to read aloud a script of instructions for the appropriate laboratory challenge. For the Control group, individuals were asked if they were comfortable and instructed to continue to watch the film. Subjects assigned to the Math challenge were asked to orally calculate a series of progressively more difficult math problems, including addition, subtraction, multiplication, division and serial problems. Finally, subjects assigned to the Interview condition were asked to complete the Daily Hassles Questionnaire and then be interviewed about their responses on this scale. Both laboratory challenges required approximately 15 minutes to complete. The stress of both laboratory challenges was enhanced by informing subjects that their responses would be filmed. Moreover, they were asked to speak into the microphone located adjacent to their chair.

After the challenge was completed, the investigator quietly entered the experimental room and turned off the microphone and camera. Subjects in both laboratory challenge conditions were asked to continue to watch the film. Blood was automatically taken (30-35 ml over 5 min.) using the Dakmed pump at the time of needle insertion, following the 20 minute rest period (during which subjects watched the neutral video) and immediately, 15 and 45 minutes following the challenge. Subjects assigned to the Control group had the same amount of blood taken at the same times as those in the laboratory challenge groups. As with the Arithmetic and Interview groups, the experimenter entered the room on two occasions to ask the Control subjects if "everything was o.k." and to instruct them to continue to watch the film.

At the end of the procedure, subjects were given juice and cookies, as well as the questionnaire package. This package contained the identical measures as those described in Experiment 1A. Subjects were then thoroughly debriefed and were informed that they would be telephoned at a later date to set up an appointment for another sampling session.

Again, collection tubes that were used for cortisol, ACTH, prolactin and the plasma amines, contained 1% EDTA (per volume dH₂O), while heparinized tubes were used for the immune measures. Radioimmunoassays were conducted for the determination of concentrations of plasma hormones (cortisol, ACTH and prolactin), while plasma NE and Epi were determined through High Performance Liquid Chromatography procedures (as outlined previously). Lymphocyte proliferation was also determined for all sampling points.

Statistical Analyses

It was our interest to assess the amine hormonal, immune alterations over time attributable to the laboratory challenges. Accordingly, a series of 3 (Stress Treatment) x 4 (Time Relative to Challenge [where only Relaxation sample was used as the Baseline Sample]) as a analyses of variance with repeated measures were conducted on each of the plasma hormones, (ACTH, cortisol and prolactin), and the plasma amines, (NE and Epi). As suggested previously (Herbert, Coriell & Cohen, 1994), separate 3 (Stress Treatment)

x 5 (Time Relative to Challenge) x 3 (Dose of Mitogen) doubly repeated measures analyses of variance were used to assess the challenge-induced variations of Con A- and PHA-stimulated cell proliferation. Inasmuch as our primary focus was to determine the effects of the laboratory challenge on each of these biological variables (and, not a system of biological variables), a set ANOVAs were performed rather than multivariate analyses of variance (MANOVAs) (Huberty & Morris, 1989). Again, Bonferroni corrected α -levels were used to prevent the occurrence of Type I errors.

Results and Discussion

ACTH, Cortisol and Prolactin:

A 3 (Stress Treatment) x 4 (Time) repeated measures ANOVA yielded a main effect of Time, $F(3, 75) = 5.072$, $p < .01$. Overall, mean plasma ACTH values declined over the course of the laboratory session across all groups. The Stress Treatment x Time interaction approached, but did not reach statistical significance, $F(6, 75) = 2.011$, $p = .07$. Curiously, Newman-Keuls multiple comparisons ($\alpha = .05$) indicated that both the Arithmetic and Interview groups showed lower plasma ACTH values relative to the Control group (see Figure 2).

Insert Figure 2 about here

Paralleling the ACTH data, both plasma cortisol and prolactin concentrations did not vary as a function of the Stress Treatment x Time interaction, but were found to decline over the sampling period $F(4, 104; 3, 135) = 6.94$ and 16.23 , p 's $< .0001$ (see Figure 2).

Plasma Norepinephrine and Epinephrine

In contrast to the HPA hormones, plasma NE levels varied as a function of the Stressor Treatment x Time interaction, $F(8, 92) = 2.151, p < .05$. Newman-Keuls multiple comparisons indicated that the groups did not differ from one another at baseline. However, immediately following the Interview regarding subjects' negative life experiences, plasma NE levels were elevated relative to baseline and that of the remaining two groups (see Figure 3). Unlike NE, plasma epinephrine (Epi) concentrations were not affected by either laboratory challenge, $F(8, 92) < 1$.

 Insert Figure 3 about here

While the laboratory stressors employed in the present study did not influence HPA activity, the stress associated with the Interview concerning negative life experiences was sufficient to alter levels of circulating NE. The lack of an effect of the Interview on plasma ACTH and cortisol are consistent with those previously reported by Griffiths, Ravindran, Merali & Anisman (1996), but inconsistent with their findings of no changes of norepinephrine. It could be argued that changes of plasma NE in the present study were attributable to greater levels of depressive symptomatology among the subjects (whereas none of the university students who participated in Griffiths et al. (1996) study had BDI scores greater than 4). However, only 2 of our 10 Interview subjects (one male and one female) had BDI scores greater than 4 (scores = 15 and 10, respectively). Moreover, these two subjects showed attenuated increases of plasma NE relative to the 8 other Interview subjects. This observation with these 2 particular subjects is also consistent with Griffiths et al. (1996), who showed that neither the control nor the depressed subjects displayed elevations of plasma NE following the Interview. While the source for the difference of the plasma NE between the two experiments is unclear, it is

commonly observed that stressful events may elevate NE levels without provoking comparable variations of plasma cortisol or ACTH (see Henry, 1993).

Mitogen-Stimulated Lymphocyte Proliferation

Figure 4 shows the mean Con A and PHA-stimulated cell counts (c.p.m.) for the Control, Arithmetic and the Interview groups at all of the sampling times. Unlike plasma NE, neither Con A nor PHA-stimulated cell proliferation varied as a function of the Stress Treatment x Time x Dose, F 's < 1.

Insert Figure 4 about here

Experiment 2A: Influence of Depressive Symptomatology plus Complex

Laboratory Stress on Endocrine & Immune Activity

An individual's preexisting level of depressive symptomatology may influence their HPA and immune responses to subsequent stressors. Indeed, as discussed earlier, prominent alterations of HPA activation and immune activity were observed among major depressives with melancholia (see Maes, 1995). Coincidentally, this population also reported more daily hassles, showed increased stress perception and tended to favor emotion-focused types of coping (at the expense of more effective problem-focused and/or cognitive restructuring coping). It is conceivable that persons reporting mild to moderate (but not clinical) depressive symptomatology may show similar behavioral patterns as those with clinical depression. Indeed, the results of Experiment 1A support this idea. In particular, individuals who report mild to moderate depressive symptomatology may be more reactive to various forms of stress (including complex laboratory tasks) relative to individuals who do not report these symptoms. Likewise, other behavioral characteristics (e.g., increased stress perception and loneliness, and the use of inappropriate coping strategies), which are more likely to be demonstrated in the presence of depressive symptomatology, may influence endocrine and immune responses

to a stress-provoking complex laboratory task (i.e., the preparation and delivery of a videotaped speech followed by a progressively more difficult arithmetic challenge) (see Kirschbaum, Pirke, & Hellhammer, 1993).

Experiment 2A examined the influence this complex laboratory stressor on plasma endocrine alterations of cortisol, ACTH, prolactin as well as NE and Epi among subjects differing in levels of depressive symptomatology. Functional immune activity was assessed, including PHA and Con A-stimulated lymphocyte proliferation.

Methods

Subjects: Introductory Psychology students from several different classes were prescreened for the presence of depressive symptomatology using the Beck Depression Inventory. Subjects were contacted by telephone if they had a total BDI score equal to or less than 3, or greater than or equal to 9. These cut-off scores were based upon Beck & Beck's (1972) criteria, where a total BDI score of 0-4 reliably estimates none or minimal depressive symptomatology, while a score between 8-15 is equivalent to mild-moderate depression.

A total of 30 male (20.96 +/- 2.15 years) and 36 female (19.86 +/- 1.04 years) Introductory Psychology students were obtained using this BDI criteria (age range of 17-26 years). These subjects were briefly screened for the presence of medical conditions. Again, all blood sampling was conducted between 0700-1200.

Procedures: As in Experiments 1A and 1B, a registered nurse inserted a butterfly i.v. catheter into the subject's non-dominant arm. Blood was automatically taken using the Dakmed withdrawal pump.

Subjects were randomly assigned to one of four groups with approximately an equal number of males and females in each condition; Control, Expectation Control, Math/Neutral Speech, or the Math/Emotional Speech. Following 20 minutes of the neutral film, two groups of subjects were exposed to one of two complex laboratory challenges. The challenges consisted of the preparation and delivery of a 5 minute speech

on either a relatively neutral topic (the effects of television on behavior in adults and children) or an emotionally-laden topic (something that has happened to them in the past that has bothered them intensely). Immediately following the speech, both groups were required to perform a task out loud of approximately 7 minutes in length. Such a combination of a social as well as a task-oriented challenge was designed in a manner similar to the "Trier Social Stress Test" (see Kirschbaum, Pirke, & Hellhammer, 1993) with the exception that subjects in the present study were not required to perform the tasks in front of an audience. However, as in Experiment 1B, subjects assigned to either of the challenged groups were instructed to speak clearly into the microphone and to look directly into the camera. As well, subjects were able to see their reflection on the television screen during the videotaping of the challenge.

Subjects in the Expectation group were told that they would be required to prepare a 5 minute speech then perform the math challenge, but ultimately, were never exposed to the task. As in Experiment 1B, both the Expectation and the Control group simply watched the neutral film throughout the sampling period, with the investigator entering the experimental room at the same time intervals as required for the two laboratory challenge groups.

Blood samples (30-35 ml over a 5 minute period) were obtained at time 0 (needle insertion), following 20 minutes of the neutral video, and then 5 minutes and 30 minutes following the laboratory challenges.

Biological Measures: All plasma amines and hormones were assessed using the same laboratory methods as outlined in Experiment 1A. Both PHA and Con-A lymphocyte proliferation were evaluated.

Behavioral Measures: Each subject was given a package of questionnaires containing the same scales as those previously described.

Results and Discussion

Plasma ACTH, Cortisol and Prolactin

It was hypothesized that the reactivity to a complex laboratory stressor might be influenced by levels of depressive symptomatology. Thus, a series of 2 (Beck Classification) x 4 (Stress Treatment) x 4 (Time) repeated measures analyses of variance were performed to assess the influence of depressive state on subjects' HPA, sympathetic and functional immune responses following exposure to a complex laboratory challenge.

Plasma ACTH, cortisol and prolactin did not vary as a function of the BDI classification or Stress Treatment, F 's < 1.5 . Paralleling the hormonal data of Experiment 1B, the levels of plasma ACTH, prolactin and to a lesser extent, cortisol, varied over Time irrespective of BDI classification or Stress Treatment, F 's (3, 147; 3, 138) = 7.547, and 36.43, p 's $< .0001$ and $F(3, 135) = 2.52$, $p = .06$, respectively (see Figure 5). As was observed in Experiment 1B, multiple comparisons of the main effects ($\alpha = .05$) confirmed that circulating ACTH and prolactin declined over the sampling period.

 Insert Figure 5 about here

Plasma Norepinephrine and Epinephrine

Plasma Epi, but not NE, varied only with Sampling Time, $F(3, 132) = 3.457$, $p < .05$ and $F(3, 114) < 1$, respectively. Similar to the hormonal measures, the multiple comparisons ($\alpha = .05$) indicated that Epi declined across sampling period (see Figure 6). These data, as well as the hormonal data suggest that the laboratory challenges employed were not sufficient to provoke significant alterations of either circulating hormones or amines. These findings are consistent with the data from Experiment 1B, where plasma ACTH, cortisol and prolactin declined over the laboratory session, but was inconsistent with respect to the previously observed plasma Epi variations. Subjects from Experiment

1B did not exhibit changes of plasma Epi across the sampling session whereas, subjects' in the present investigation showed declines of plasma Epi levels (rather than increases, which would be expected among subjects within the arithmetic/speech groups). As will be discussed shortly, alterations of these measures within a laboratory setting are, to some extent, dependent upon the qualitative nature of the laboratory challenge.

 Insert Figure 6 about here

Mitogen-Stimulated Cell Proliferation

Both Con A- and PHA-stimulated cell proliferation varied over the Time x Dose of Mitogen interactions, $F's(6, 168; 6, 186) = 3.052$ and 2.31 , $p's < .05$, respectively (see Figure 7). The multiple comparisons indicated that there was a modest increase of cell

-----
 Insert Figure 7 about here
 -----

proliferation of the lymphocytes stimulated with 1.0 ug of Con A at the 30 minute post-challenge sampling time. In contrast, modest reductions of 0.625 and 1.25 ug PHA-stimulated cell counts were observed between needle insertion (Time 0) and the 20 minute relaxation sample. While the importance of these modest changes of immune activity are unclear, it seems that immune activity is sensitive to even mild environmental challenges, such as the insertion of the needle and/or the anticipation or the cessation of a stressful stimulus (e.g., the end of the laboratory task).

Neither Con A nor PHA-stimulated cell proliferation varied as a function of the Stress Treatment nor any of the interactions involving this variable. Thus, it appears that the complex challenges were not sufficient to engender alterations of either hormonal, sympathetic or immune activity. Moreover, these data also demonstrate the necessity of using either a more severe or more *socially relevant* challenge to study the effects of

acute stressors on endocrine and immune activity. Indeed, Kirschbaum et al., (1993) observed marked increases of plasma cortisol, NE and Epi following the "Trier Social Stress Test", which, like the present investigation, utilized the combination of a cognitive task plus the preparation and delivery of a speech on a specified topic. However, in addition to the task requirements, subjects were required to perform the speech component in front of a "panel" of three confederates, and thus, were exposed to an additional (and for some subjects, potentially very stressful) social stressor (Kirschbaum et al., 1993). Indeed, we only observed changes of plasma NE in response to the Interview (see Experiment 1B), which included a socially stressful component (i.e., talking about negative experience of a personal nature in front of an interviewer). Therefore, it is conceivable that an effective way in which to elicit significant physiological responses to laboratory challenge(s) may be to include a socially stressful component which is specific to the population examined.

Experiment 2B: Influence of Examination Stress on Immune & Neuroendocrine Activity Among University Students

Variable results have been obtained concerning functional immune alterations associated with naturalistic stressors, such as the anticipation of academic examinations. For instance, while examination stress has been associated with decreases of both NK cytotoxicity (Glaser, et al., 1986; Kang, Coe, & McCarthy, 1996; Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984) and cell proliferation (Dorian, et al., 1982; Glaser, et al., 1993), other reports demonstrated either no effect or even opposite effects, at least with respect to cell proliferation (Kang, et al., 1996; Kang et al., 1997; Whitehouse et al., 1996). Such variability may be a function of the different populations studied (medical students vs. first year university students and adolescents), the time of immune measurement relative to the examination (Dorian, et al., 1982; Kang et al., 1996; Whitehouse, et al., 1996), and/or the perceived importance (and hence stressfulness) of

the examination. Indeed, such variables have been shown to influence endocrine responses to examination stress (e.g., Armario, Merti, Molina, Depablo, & Veldes, 1996).

Accordingly, Experiment 2B was conducted to assess potential changes of endocrine/immune measures immediately prior to a final Introductory Psychology examination relative to a nonstressed baseline period. In addition to measuring the perceived stressfulness of the psychology examination, students' initial vs. final expectations of their academic performance were examined to assess whether these expectations influenced the hormonal and immune measures. Moreover, the relationship between the of subjects' prior stressor history, as well as the use of particular coping strategies, and the alterations of endocrine/immune activity in anticipation of the academic examination was assessed.

Subjects

Subjects from Experiments 1B and 2A (i.e., those that had been enrolled in the laboratory stressor studies and had also provided a baseline blood sample during a stress-free period) were contacted by telephone and asked if they would be willing to provide a blood sample approximately 1 hour prior to their final Introductory Psychology examination. Of the 111 subjects who were telephoned, 92 agreed to give blood for this portion of the study. The data from this part of the experiment were collected over a period of 2 years.

Procedures

On the day of the academic examination, subjects were greeted by the investigator and were then asked to complete the Perceived Stress Scale (Cohen, Karmarck, & Marmelstein, 1983) as well as the Examination Questionnaire (see Appendix B). This questionnaire contained items which directed subjects to indicate: their present academic performance in Introductory Psychology (i.e., letter grades; A-, B+, C+ etc.), their expected/hoped for grade in the course, their initial academic goals with respect to this course, the overall performance they would be satisfied with, and finally, the perceived

stress of the impending Introductory Psychology Examination using a 7-point Likert scale (see Appendix B).

After completing these scales, blood sampling procedures commenced. Since subjects could not be kept in the laboratory for an extended duration (owing to their impending academic examination), a single-stick blood sample (approximately 30-35 ml) was drawn by the nurse using a 21 gauge butterfly needle attached to a 60 ml sterile syringe (instead of using the Dakmed pump as previously described). Immediately following this procedure, subjects were debriefed.

Plasma cortisol, ACTH, NE, Epi and lymphocyte proliferation measures were analyzed for all subjects. However, only subjects from Experiment 2A had macrophage/neutrophil activity measured as chemiluminescence equipment was not available when subjects from Experiment 1B were tested.

Statistical Analyses

Inasmuch as examination blood samples were taken immediately following needle insertion, a series of one-way repeated measures analyses of variance (or paired t-tests, for analyses where there was no grouping variable) were conducted for each of endocrine and immune measures using the Time 0 blood sample (needle insertion at the baseline period of Experiment 1B and 2A) as the appropriate baseline measure. These analyses were performed to determine which, if any, of the biological variables varied in the same individuals between the nonstressed baseline sampling period and immediately prior to the impending Introductory Psychology examination.

It was expected that some individuals would show negligible changes of the neuroendocrine/immune measures prior to the anticipated Introductory Psychology examination, whereas others would exhibit exaggerated biological responses. Again, it was of interest to assess whether certain behavioral variables thought to be associated with biological reactivity might account for interindividual differences of the biological responses to a naturalistic stressor. Therefore, simple regression analyses were performed

to determine whether subjects' levels of Perceived Stress and/or level of exam-specific stress perception might predict the alterations of endocrine and immune activity associated with examination. As well, the relationship(s) between subjects' initial expectancies of academic performance in Introductory Psychology (relative to their perceived performance in the course) and the changes of immune and endocrine activity were assessed .

Finally, as in Experiment 1A, the relationship(s) between individuals' prior stressor history and/or use of coping strategies and the biological alterations attributed to the examination were determined using a series of hierarchical regression analyses. Again, to determine whether these stressor-related variables could predict the alterations of endocrine and immune activity *above and beyond* that which might be attributable to individual differences of depressive symptomatology, subjects BDI scores were forced into the hierarchical regressions first, followed by Major Life Events or Daily Hassles. This procedure was repeated for each of the coping strategies indexes.

As in Experiment 1A, only the composite coping strategies subscales were used, including Emotional Expression plus Social Support Seeking, Emotional Containment plus Passivity, and Individual Coping plus Cognitive Restructuring to reduce the number of predictor variables in the hierarchical regressions. These analyses included the percent change values for each of the endocrine and immune measures as the dependent variable. The percent or proportionate change of these measures was calculated by obtaining the ratio of the examination value divided by the baseline value, then multiplying by 100.

It might be noted that *both* the percent change *and* the absolute change values were calculated (where the absolute change value was equal to the particular biological measure [e.g., plasma ACTH] obtained immediately prior to the examination minus the baseline value) and hierarchical regression analyses were performed using either the percent change or absolute change values (for each respective biological measure) as the dependent variable. Not unexpectedly, these hierarchical regression analyses indicated

that using either of these change scores as the dependent measure yielded equivalent results. Accordingly, only the regression analyses using the percent change values as the dependent variable will be shown, unless the two measures yielded appreciably different results.

Results and Discussion

Variations of Endocrine & Immune Activity Associated with an Examination

ACTH, Cortisol & Prolactin

Inasmuch as a portion of subjects initially tested in the morning subsequently had blood samples taken prior to an afternoon Introductory Psychology examination, the statistical analyses also evaluated whether the change of the time of sampling (e.g., having the Baseline sample obtained in the morning, and then having the examination sample obtained in the afternoon) would affect the patterns of endocrine and immune activity. In fact, the analysis of variance of the plasma ACTH levels indicated a significant Time x Sampling Period interaction, $F(1, 70) = 6.497$, $p = .01$. The multiple comparisons ($\alpha = .05$) confirmed that among subjects initially tested in the morning and from whom a blood sample was taken prior to a morning academic examination, ACTH levels increased appreciably. In contrast, there was no such increase among subjects from whom a baseline blood sample was initially taken in the morning and an afternoon blood sample taken in anticipation of the exam.

Plasma prolactin levels also varied as a function of the Time x Sampling Period interaction, $F(1, 70) = 5.95$, $p < .05$. Paralleling the ACTH data, plasma prolactin levels were also shown to increase prior to the Introductory Psychology examination. However, plasma cortisol neither varied as a function of the Sampling Period or the Time x Sampling Period interaction, $F's < 1$.

Inasmuch as the responsivity of the HPA axis to stressful stimuli is, to some extent, dependent upon the sampling time (due to its circadian rhythmicity), it may be inappropriate to compare individuals tested at two different sampling periods (i.e.,

morning vs. afternoon). Thus, the subsequent analyses of variance used to assess the influence of the Introductory Psychology examination on HPA, sympathetic and immune activity only included subjects who had a morning examination. Parenthetically, this methodological issue concerning the consistency of the time of blood sampling was addressed in the subsequent study (Experiment 3).

Figure 8 shows the plasma concentrations of ACTH, prolactin and cortisol measured at Baseline and immediately prior to the Introductory Psychology examination. As discussed previously, multiple comparisons confirmed that plasma concentrations of both ACTH and prolactin increased by about 30-35% over the two sampling periods (among the subjects who were tested solely in the morning). In contrast to ACTH and prolactin, levels of plasma cortisol did not change between the two sampling periods.

Insert Figure 8 about here

Of particular interest for the present investigation was the finding that the changes of plasma prolactin observed prior to the Introductory Psychology examination varied according to the Beck Classification. It will be recalled from Experiments 1A that subjects were classified according to their total Beck Depression Inventory (BDI) scores, as either "Low" (0 to 3), "Moderate" (4 to 8) and "High" (9 or greater). One-way between-groups analyses of variance showed that the percent change of plasma levels of prolactin (between the baseline and pre-exam sampling periods) varied according to the BDI classification $F(2, 86) = 5.95$ $p < .01$ (see Figure 9). Multiple comparisons ($\alpha = .05$) confirmed that individuals with Low BDI scores showed only a moderate, although statistically significant, increase (approximately 22%) of plasma prolactin, whereas individuals with High BDI scores (9+) displayed a more considerable elevation of this hormone (about 66%). In contrast, individuals with Moderate BDI scores (scores between

4-8) showed a small decline of plasma prolactin levels (about 8%) relative to baseline values.

 Insert Figure 9 about here

In contrast to prolactin, the alterations of plasma ACTH and cortisol did not differ as a function of the BDI classification, F 's < 1.50 . Yet, the percentage changes of ACTH were aligned with the exam-related variations of prolactin ($r = +.53$), $F(1, 49) = 19.85$, $p < .001$.

Norepinephrine and Epinephrine

As in the case of ACTH and prolactin, the analyses of variance indicated that plasma NE and Epi levels increased between the two sampling periods, F 's(1,43; 1, 45) = 8.68, 6.92, p 's $< .01$. However, as seen in Figure 10, the magnitude of these increases was relatively modest (approximately 25%). In contrast to plasma prolactin, the pattern of these changes of plasma NE and Epi did not vary as a function of BDI classification, F 's < 1 .

 Insert Figure 10 about here

Mitogen-Stimulated Lymphocyte Proliferation:

The analysis of variance indicated that Con A-stimulated lymphocyte proliferation varied as a function of the interaction between the Sampling Period and the Con A dosage, $F(2, 100) = 7.214$, $p < .01$. Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple effects comprising this interaction indicated that Con A-stimulated cell proliferation (1.0 and 2.0 ug doses) was elevated prior to the Introductory Psychology examination relative to the baseline period (see Figure 11). At the highest Con A dosage (5.0 ug), the effects of the exam were not statistically significant.

PHA-stimulated cell proliferation also varied as a function of the Sampling Period x Dose interaction, $F(2, 98) = 5.803$, $p < .01$. However, in contrast to the effects seen in Con A-stimulated lymphocytes, the anticipation of the Introductory Psychology examination was not associated with an increase of cell proliferation in PHA-stimulated lymphocytes. In fact, the multiple comparisons ($\alpha = .05$) confirmed that a slight, but significant decline (approximately 15%) of cell proliferation was observed prior to the academic examination among cultures stimulated with 2.5 ug of PHA. There were no significant differences of cell proliferative activity between baseline and the examination at the lower doses of PHA.

Insert Figure 11 about here

Predictors of Endocrine and Immune Alterations Associated with an Impending Introductory Psychology Examination

The primary focus of the present investigation was to examine the immune alterations associated with both laboratory and naturalistic stressors, and to assess the behavioral correlates of the stress-related changes of immune activity. Nevertheless, in addition to the immune alterations, changes of HPA and sympathetic activity were also observed prior to the Introductory Psychology examination. Again, however, the changes of hormonal, sympathetic and immune activity were not observed in all subjects. To be certain, the interindividual variability of these exam-related alterations might parallel the variability of subjects' behavioral profiles. Moreover, it was possible that subjects who were classified as either Moderate or High in depressive symptomatology (as defined by their BDI scores), had behavioral profiles distinct from those subjects with "Low" BDI scores. Additionally, the subjects with "Moderate" and, more likely, "High" BDI scores might also have distinct endocrine, sympathetic and/or immune profiles, which, in

combination with their respective behavioral profiles, could render them more susceptible to environmental challenges.

Thus, regression analyses were conducted to determine whether a) the endocrine changes associated with the stress of the Introductory Psychology examination were predictive of the immune alterations and, b) whether subjects' prior stressor history as well as the use of coping strategies were predictive of the changes of endocrine, sympathetic and/or immune activity associated with the impending academic examination over and above that which could be attributable to levels of depressive symptomatology.

Alterations of Endocrine and Sympathetic Activity Predict the Changes of Immune Activity Prior to an Introductory Psychology Examination

The percent of plasma ACTH associated with the examination was positively correlated with percent changes of plasma prolactin ($r = +.53$), $F's (1, 53) = 19.85$, $p < .001$. In contrast, neither the alterations of plasma ACTH nor prolactin were related to either the alterations of plasma cortisol, NE or Epi observed prior to the Psychology exam, $F's(1, 43) < 1.5$, $p's > .05$. Thus, while it has been suggested that stressor-related changes of circulating cortisol contribute to HPA dysfunction and/or immune activity, these hierarchical regression analyses indicated that the cortisol changes were likely independent of the alterations of plasma ACTH and prolactin. Moreover, the changes of plasma cortisol were unrelated to changes of either NE or Epi on the day of the exam, $F's < 1$.

Simple regression analyses were performed to determine whether the alterations of the plasma hormones predicted the exam-related changes of lymphocyte proliferation. The alterations of cell proliferation were not predicted by the changes of plasma cortisol, prolactin, NE or Epi, $F's < 1.5$.

Curiously, the *absolute* changes of prolactin significantly predicted the absolute alterations of cell proliferation of lymphocytes stimulated with 1.0 and the 2.0 ug Con A

(β 's = .47; .47; sr^2 's = .22; .25), F 's(1, 29) = 7.48 and 7.65, p 's < .05, respectively (see Table 22). Thus, subjects who exhibited greater elevations of prolactin were more likely to show greater elevations of cell proliferative activity immediately prior to the examination challenge.

 Insert Table 22 about here

Behavioral Correlates of Alterations of Neuroendocrine & Immune Activity Associated with the Impending Introductory Psychology Examination

As mentioned previously, we were interested in assessing whether the endocrine and/or immune changes observed prior to the Introductory Psychology examination were influenced by subjects' previous stressor history and/or their use of coping strategies. It will be recalled that subjects' previous stressor history was evaluated using both the Life Events Scale (Paykel, Prusoff, & Uhlenhuth, 1971), the Daily Hassles Scale (Kanner, Coyne, Schaefer, & Lazarus, 1981), each of which, measure both the Frequency and Intensity/Severity of the event or hassle. As in Experiment 1A, only the correlations between the Intensity/Severity subscales and the percent hormonal/immune changes were reported. Again, this procedure was undertaken to simplify the following results and discussion section of Experiment 2B.

Plasma Cortisol, ACTH and Prolactin

Although plasma cortisol concentrations were not affected by the impending Psychology examination, after the influence of BDI scores were accounted for, the Severity of Daily Life Hassles negatively predicted the change of this measure, (β = -.46; sr^2 = .16), F (1, 43) = 7.39, p < .01 (see Table 23). Indeed, approximately 16 percent of the variance of the changes of plasma cortisol could be uniquely attributed to the Severity of these Daily Life Hassles. Moreover, subjects' level of depressive symptomatology plus the Intensity of their Daily Life Hassles did not predict significantly more variance of the

changes of this measure. These finding indicates that previous stressor history, in the form of daily minor hassles, may influence subsequent cortisol responses to impending challenges among individuals who are not *clinically* depressed.

 Insert Table 23 about here

It is of particular interest that, while the intensity of subjects' total Major Life Events did not predict the alterations of plasma cortisol, particular types of Major Life Events were predictive of these hormonal changes. Simple regression analysis indicated that the Intensity of Exits from the Social Field (i.e., death of a close family member or friend, the physical separation from a significant dating partner and/or the actual cessation of a significant dating relationship) were negatively related the changes of plasma cortisol ($r = -.33$), $F(1, 45) = 4.89$, $p < .05$. Curiously, the addition of BDI as an predictor did not account for more unique variance of the cortisol changes. Thus, irrespective of subjects' level of depressive symptomatology, it seemed that Major Life Events involving the separation and/or cessation of important social relationships, influenced subjects' subsequent cortisol responses to the Introductory Psychology examination (see Table 23).

Like the cortisol data, the Severity of Daily Life Hassles was negatively associated with the percent change of prolactin concentrations ($\beta = -.44$; $sr^2 = .20$), $F(1, 45) = 8.01$, $p < .01$ (see Table 23). Subjects who reported more Severe Daily Hassles showed attenuated changes of both plasma cortisol and plasma prolactin levels prior to a subsequent stressor. In contrast to plasma cortisol and prolactin, subjects' previous stressor history was not associated with the changes of plasma ACTH. Moreover, neither Perceived Stress, level of depressive symptomatology, subjects' expectations of their academic performance nor levels of examination-specific stress perception, predicted the alterations of plasma ACTH, cortisol or prolactin, F 's < 3.00 .

Like stressor history, it was expected that subjects' use of coping strategies would be associated with the endocrine responses to the academic challenge. Hierarchical regression analyses showed that use of Emotional Expression plus Social Support Seeking was negatively associated with the changes of prolactin prior to the exam ($\beta = -.41$; $sr^2 = .13$), $F(1, 43) = 5.72$, $p < .05$ (see Table 24). Moreover, multiple regression analysis indicated the combination of subjects' BDI together with the use of Emotional Expression plus Social Support Seeking accounted for almost 14% of the variance of the prolactin changes ($R^2 = .14$). In contrast to prolactin, neither the use of Emotional Expression plus Social Support Seeking, Emotional Containment plus Passivity nor Individual Coping plus Cognitive Restructuring predicted the alterations of plasma ACTH or cortisol.

 Insert Table 24 about here

In summary, the analyses of these behavioral data indicated that previous stressor history, particularly Daily Hassles, influenced subjects' alterations of cortisol and prolactin immediately prior to the Introductory Psychology examination. In fact, subjects' with more severe Daily Life Hassles exhibited smaller elevations of plasma cortisol immediately prior to the examination. Similarly, exposure to socially relevant Major Life Events, such as the separation and/or cessation of significant interpersonal relationships, was also associated with reduced changes of plasma cortisol. However, other than subjects' use Emotional Expression plus Social Support Seeking, none of the behavioral indices (depressive symptomatology, perceived stress, or performance expectations associated with the exams) predicted the changes of the stress-related hormones.

Plasma Norepinephrine and Epinephrine

Hierarchical regression analyses indicated that the change of plasma Epi was negatively related to the Severity of Daily Hassles, ($\beta = -.44$; $sr^2 = .14$), $F(1, 43) = 7.13$, p

< .05. Consistent with the cortisol and prolactin data, subjects who reported having experienced more severe Daily Hassles had reduced changes of plasma Epi prior to the Introductory Psychology examination (see Table 25).

 Insert Table 25 about here

In contrast to plasma Epi (as well as cortisol and prolactin) neither the intensity of Major Life Events nor the severity of Daily Life Hassles predicted changes of plasma NE. Yet, their stress perception (Perceived Stress Scale) significantly predicted the alterations of this amine ($\beta = .54$, $sr^2 = .14$), $F(1, 40) = 6.48$, $p < .05$. Approximately 14 percent of the variability of the changes of circulating NE prior to the examination challenge could uniquely attributed to Perceived Stress (see Table 26).

 Insert Table 26 about here

In general, hierarchical regression analyses indicated that neither subjects' use of Emotional Expression plus Social Support Seeking, Emotional Containment plus Passivity nor Individual Coping plus Cognitive Restructuring significantly predicted the exam-related NE or Epi alterations. Nevertheless, simple regression analyses indicated that subjects' use of Emotional Expression was positively related to the NE changes ($r = +.33$), $F(1, 39) = 4.93$, $p < .05$, whereas their use of Problem Solving strategies negatively predicted the changes of plasma Epi ($r = -.30$), $F(1, 40) = 3.72$, $p = .06$.

These data indicate that, again, subjects' who reported having experienced more severe Daily Hassles exhibited moderated increases of plasma Epi prior to the Introductory Psychology examination. Moreover, use of specific coping strategies (i.e., Emotional Expression and Problem Solving) were related to the changes of sympathetic activity. Not surprisingly, the increased use of Emotional Expression was associated with

greater elevations of plasma NE, whereas the use of Problem Solving strategies was associated with moderated increases of plasma Epi.

Mitogen-Stimulated Cell Proliferation

As in the previous experiments, hierarchical regression analyses were conducted to examine the influence of previous stressor history on the proportionate changes of Con- A and PHA-stimulated cell proliferation after the effects of subjects' BDI scores were statistically removed. These analyses indicated that the Intensity of Major Life Events were associated with changes of Con A-stimulated cell proliferation observed prior to the Introductory Psychology examination, ($\beta = -.31$, $sr^2 = .09$), $F(1, 50) = 4.78$, $p < .05$ (see Table 27).

Insert Table 27 about here

In contrast to the hormonal data, neither the use of Emotional Expression plus Social Support Seeking, Emotional Containment plus Passivity nor the use of Individual Coping plus Cognitive Restructuring predicted the changes of either Con A or PHA-stimulated cell proliferative activity that were observed prior to the examination.

Quality of Life Predictors Exam-Related Alterations of Endocrine & Immune Activity

It will be recalled from Experiment 1A that some of the Quality of Life indices, including Life Satisfaction and Energy, were related to the basal levels of functional immune activity. Indeed, during nonstressed conditions levels of Energy were positively correlated with functional immune activity, whereas Life Satisfaction was negatively associated with immune activity. It was considered that certain components of Quality of Life might be related to the alterations of endocrine and/or immune activity that occurred prior to the Introductory Psychology examination. For consistency, hierarchical regression analyses were conducted with subjects' BDI scores being forced into the regression equation first. Moreover, these analyses were performed using the data from

subjects who had morning blood samples obtained at both sampling periods (i.e., the nonstressed Baseline and immediately prior to the Introductory Psychology examination).

These hierarchical regression analyses indicated that the *absolute* changes of plasma epinephrine were positively associated with Life Satisfaction ($\beta = .48$, $sr^2 = .10$), $F(1, 52) = 5.71$, $p < .05$ (see Table 28). In contrast, none of the Quality of Life variables significantly predicted the changes of plasma ACTH, cortisol or prolactin.

Insert Table 28 about here

Curiously, basal levels of Energy were negatively associated with the *absolute* changes of 2.0 ug Con A-stimulated cell proliferative activity ($\beta = -.45$, $sr^2 = .11$), $F(1, 39) = 4.63$, $p < .05$ (see Table 29). In effect, it appeared that Energy levels were differentially related with immune activity during nonstressful and stressful conditions. That is, while Energy was positively associated with basal immune measures, this variable was *negatively* associated with absolute changes of immune activity observed prior to the examination.

Insert Table 29 about here

Experiment 3: Influence of Anticipation of Exams on Immune & Neuroendocrine Activity Among University Students: Time Course Assessments

Experiment 2B examined the influence of a final Psychology examination (a naturalistic stressor) on several endocrine and functional immune measures. However, it should be noted that this particular examination was invariably scheduled at the end of the testing period. Additionally, the majority of subjects who participated in Experiment 2B had already undergone as many as four or five other examinations prior to the final Introductory Psychology examination. Thus, it is conceivable that subjects: a) may have

perceived this examination as a signal of the cessation of a stressful period and, b) may have perceived earlier examinations as being more difficult, and hence, the Introductory Psychology examination may have represented a decline in stressor severity. Moreover, it is possible that the repeated examinations (prior to the Introductory Psychology exam) elicited effects similar to those noted following chronic repeated stressor exposure (i.e., adaptation).

In view of these aforementioned issues, Experiment 3 examined the potential endocrine and immune changes (relative to baseline) among Introductory Psychology students on the afternoon prior to the first examination of the testing schedule. Again, prior to taking the blood measures, the perceived stressfulness of this first examination was measured, as was the students' initial vs final expectations of their academic performance for the course in question. Moreover, as in the preceding study, subjects' previous stressor history and/or the coping strategies they used were examined to determine whether these behavioral variables would account for the variability of changes of endocrine and/or immune activity that might be associated with the *initiation* of the examination period.

Methods

Subjects

A total of 31 male (20.62 ± 1.80 years) and 26 female (21.16 ± 1.64 years) subjects were obtained from the Carleton University Introductory Psychology pool. All subjects were contacted by telephone and asked if they would be willing to give 2 blood samples, one taken approximately 4-6 weeks prior to the examination period (i.e., the baseline sample - an afternoon appointment). The second sample was obtained the afternoon prior to their first examination. During their baseline session, subjects were informed they would also be required to fill out some questionnaires describing their mood states, negative and positive events in their lives, and the coping strategies they used. As in the preceding experiments subjects were excluded for any medical conditions

that might influence endocrine or immune measures, as well as the presence of any viral illness in the preceding two weeks. Then, each subject was given an appointment for their baseline blood sampling session. As in the previous experiments, subjects were asked to refrain from any food or beverage (with the exception of water) for at least 2 hours prior to each sampling session. Immediately following this baseline session, subjects were given the questionnaire package and asked to complete the questionnaires within 48 hours. Again, as with previous experiments, all subjects received academic/experimental credit for their participation.

Procedures

During the baseline visit, and following informed consent being obtained, subjects were directed to a comfortable chair in the sampling room where a description of the blood collection procedures was given. Blood was drawn from the antecubital fossa of the subject's non-dominant arm (30-35 ml) by the nurse using a 21 gauge butterfly needle attached to a 60 ml sterile syringe. Immediately following the baseline session, subjects were given the package of questionnaires (as previously described).

Scales included within this package were the same as those outlined in Experiments 1A and 1B with the addition of the Mastery Scale (Pearlin & Schooler, 1978; see Appendix C). This scale which was made available to our laboratory prior to beginning the second portion of the present investigation. This scale is a 7-item scale which assesses the extent of which an individual perceives that he or she can control or master the events or problems he or she may experience. Subjects are asked to indicate how strongly they agree or disagree with the items on a 1 - 5 scale. Higher scores reflect a greater sense of mastery.

Prior to obtaining the pre-exam blood sample, subjects were asked to complete the Perceived Stress Scale (Cohen, et al., 1983) and the Examination Questionnaire (as described in Experiment 2B - the Introductory Psychology examination). Appointment times for this sampling session were all ± 0.5 hour of subjects' previous baseline times

(i.e., a subject tested at 1300 h during the baseline session, would have pre-exam blood samples taken between 1230-1330 h). Again, 30-35 ml blood was obtained during this session. Subjects were then debriefed.

The blood measures included the HPA hormones, including plasma cortisol, ACTH and prolactin using the radioimmunoassay procedures previously described. The functional immune measures included Con A- and PHA-stimulated lymphocyte proliferation as well as macrophage and neutrophil activity.

Statistical Analyses

A series of one-way repeated measures analyses of variance were conducted to determine the alterations of endocrine and functional immune measures between the baseline and pre-exam sampling periods. As well, hierarchical regressions were conducted (again with BDI scores entered first into the regression equations) to assess whether stressor history and/or use of coping strategies were associated with the magnitude and/or direction of exam-related changes of biological activity. It should be noted that two sets of subjects were tested. The first set of subjects provided a blood sample prior to their first *midterm* examination in December, whereas the second group of subjects provided their blood sample prior to their first *final* examination in April.

It was likely that the two groups were not equivalent in terms of the number of exams they had written (e.g., subjects who gave a blood sample prior to their first midterm examination were likely exposed to fewer examinations relative to the subjects who donated a sample prior to their first *final* examination). Moreover, it was possible that the two exams (midterm vs. final) may have been interpreted differently in terms of their stressor quality (the latter likely being more severe). Finally, these two examination sampling periods coincided with different seasons (winter vs. spring), which may have impacted on neuroendocrine or immune functioning. Accordingly, separate statistical analyses were performed for each set of subjects. Bonferroni corrections were used to achieve more conservative α -levels.

Results and Discussion

Plasma ACTH, Cortisol and Prolactin:

Figure 12 shows the mean plasma concentrations of ACTH, cortisol and prolactin among subjects tested at Baseline and prior to their respective *midterm* examinations. The levels of plasma ACTH on the afternoon prior to the examination did not differ relative to baseline values, $F's < 1$.

Insert Figure 12 about here

Inasmuch as neuroendocrine responses may have been related to basal mood states (as described earlier), separate analyses were conducted to assess the effects of the academic examination in subjects who differed with respect to BDI scores. There were few subjects ($n = 5$), however, who had total BDI scores between 4 and 8. Accordingly, in order to maintain sufficient power, the analyses of variance only included subjects with either Low or High BDI scores. Interestingly, the plasma cortisol variations between Baseline and the first midterm examination varied as a function of Beck classification, $F(1, 21) = 5.67$, $p < .05$. Newman-Keuls multiple comparisons ($\alpha = .05$) confirmed that subjects with Low BDI total scores (0-3) showed a moderate increase of cortisol concentrations prior to their first *midterm* examination, relative to baseline whereas subjects with High BDI scores showed a slight reduction of cortisol concentrations (see Figure 13).

In contrast to plasma cortisol, neither ACTH nor prolactin levels varied as a function of the sampling period (baseline vs. exam) or with the BDI classification.

Insert Figure 13 about here

Figure 14 shows the mean plasma concentrations of ACTH, cortisol and prolactin at Baseline and the afternoon prior to the *final* exam. Consistent with the midterm examination data, neither the plasma ACTH, cortisol nor prolactin levels varied $F's < 1$ as a function of the sampling period (baseline vs. final exam). Moreover, plasma levels of these hormones did not vary as a function of the Time x BDI classification interaction.

 Insert Figure 14 about here

In addition to testing subjects prior to their first respective *final* examination, 10 of the 23 subjects (44%) provided a third blood sample 24 hrs after the first exam or 10-14 days after the entire examination period. Thus, separate statistical analyses were performed for data collected from subjects who provided the third blood sample. Again, these analyses indicated that neither plasma ACTH, cortisol nor prolactin varied as a function of Time (3 sampling sessions), BDI classification or the interaction between these variables, $F's < 2.00$.

PHA and Con A-stimulated Lymphocyte Proliferation

Figures 15 and 16 illustrate the Con A and PHA-stimulated cell proliferative activity among of (a) subjects tested the afternoon prior to their first *midterm* examination (see Figure 15) and, (b) subjects tested the afternoon prior to their first *final* examination (see Figure 16).

 Insert Figures 15 and 16 about here

The analyses of variance (Sampling Period x Dose of Mitogen) yielded a main effect of Sampling Period, $F's(1, 22)$, 10.90 and 34.14, $p's < .001$, for Con A and PHA-stimulated cell proliferation, respectively. The multiple comparisons ($\alpha's = .05$) confirmed that subjects tested the afternoon prior to their first *midterm* examination

displayed increases of lymphocyte proliferation relative to baseline values at each of the Con A and PHA doses (see Figure 15).

As in the case of the blood samples taken prior to the midterm examination, Con A-stimulated cell proliferation in samples taken prior to the *final* examination were found to vary as a function of the Sampling Period, $F(1, 23) = 31.34$, $p < .001$. Similar to the midterm examination, cell proliferation was elevated prior to the final examination at all doses of Con A (see Figure 16).

Among 0.625 and 1.25 ug PHA-stimulated cell lymphocytes, there were no differences of proliferative activity between baseline and prior to the final examination. However, there was a modest, but significant increase (13%) of 2.5 ug PHA-stimulated cell proliferation. As a result of the PHA concentration-dependent effects of the examination, the interaction between these variables was found to be statistically significant, $F(2, 44) = 4.96$, $p = .01$. Thus, it would appear that while the anticipation of an academic examination was associated with elevations of Con A-stimulated cell proliferation, irrespective of the severity of the exam, the effects with respect to PHA-stimulated cell proliferation were very modest. As will be discussed later, such an outcome may simply be a reflection of the particular mitogen dosages employed (see Figure 16).

Among the subjects who provided a blood sample 10 - 14 days following the completion of the *final* examination period, both the Con A and PHA-stimulated cell proliferation varied across the Sampling Periods, $F's(4, 36) = 3.80$ and 6.63 , $p's < .01$. The multiple comparisons ($\alpha = .05$) confirmed that in this subset of students, Con A-stimulated cell proliferation was elevated on the afternoon prior to the exam (as it had been for the entire set of subjects; $n=23$). These subjects, however, did not show any changes of PHA-stimulated cell proliferation at this time. Interestingly, a marked decline of both Con A (all doses) and PHA-stimulated lymphocyte proliferation was evident 10 - 14 days after the examination period relative to that observed prior to the exam (all Con

A and all PHA doses; more evident at the 2.5 ug PHA dose) and at baseline (2.0 and 5.0 ug Con A doses and all PHA doses; see Figure 17).

 Insert Figure 17 about here

Commensurate with the earlier experiments, cell proliferation associated with an academic examination was not related to BDI. Specifically, the analyses of variance indicated that cell proliferative activity did not vary as a function of BDI classification or any of the interactions involving this variable, $F's < 1$.

Macrophage/Neutrophil Activity:

As with cell proliferation, neutrophil and macrophage activity was determined at baseline and prior to the first midterm or first final academic examination. Figure 18 illustrates the macrophage and neutrophil activity at baseline and prior to the *midterm* examination period. Paired-t-tests indicated that neither neutrophil nor macrophage activity were affected by the midterm examination relative to baseline, $p's > .05$.

 Insert Figure 18 about here

Figure 19 shows the neutrophil and macrophage activity measured at baseline and the afternoon prior to the *final* examination. In contrast to the neutrophil data obtained prior to the midterm, a significant reduction of neutrophil activity was found prior to the *final* examination, $t(22) = 22.37$, $p < .05$. However, macrophage activity did not vary between the 2 sampling periods, $p > .05$.

 Insert Figure 19 about here

Figure 20 shows the activity of macrophages and neutrophils among subjects who gave a blood sample at baseline, prior to their final examination and 10-14 days after the entire exam period. A one-way analysis of variance indicated that neutrophil activity varied over the Sampling periods, $F(2, 16) = 5.99$, $p = .01$. The multiple comparisons confirmed that relative to baseline, the reduction of neutrophil activity 24 hr prior to the examination did not reach statistical significance, likely owing to the relatively small number of subjects tested, coupled with the large interindividual variability observed during the baseline sampling period. Interestingly, however, relative to baseline and the pre-examination period, there was a significant increase of neutrophil activity 10 to 14 days after the completion of the final examination period. In contrast, relative to baseline, there were no changes of macrophage activity either before or 10-14 days following the cessation of the final examination period, $F's < 1.5$.

 Insert Figure 20 about here

Endocrine Predictors of Exam-Related Immune Alterations

As in the case of the analyses obtained from subjects prior to the final Introductory Psychology examination (Experiment 2B), the endocrine correlates of the immune alterations associated with the midterm and the final examinations periods were explored. In order to assess whether the exam-related changes of either plasma ACTH, cortisol and prolactin were related to the alterations of functional immune activity, both the percent and absolute change values were calculated (as previously described in Experiment 2B). As in Experiment 2B, the regression analyses indicated that using either the percent or absolute change values as the dependent variable yielded similar findings. Accordingly, only the analyses involving the percent changes of endocrine and/or immune activity are reported. However, in the cases where the regression analyses using

percent and absolute change values yielded different patterns, the regressions which included the absolute changes values (as the dependent measure) are shown.

The hierarchical regression analyses (with BDI scores entered first into the regression equations) indicated that neither the percent changes of ACTH, cortisol nor prolactin predicted the changes of Con A or PHA-stimulated cell proliferation observed prior to their first midterm examination, $F's < 2.00$. Moreover, the alterations of these HPA hormones did not predict the changes of macrophage or neutrophil activity, $F's < 2.00$.

Among subjects who provided a blood sample prior to their *final* examination, the changes of prolactin were related to the changes of functional immune activity. Indeed, the alterations of prolactin were positively associated with the 1.0 ug Con A-stimulated cell proliferation ($\beta = .51$, $sr^2 = .25$), $F(1, 18) = 5.47$, $p < .05$ (see Table 30). In contrast to the changes of prolactin, neither the changes of ACTH nor cortisol predicted the alterations of immune activity, including neutrophil and macrophage activity, $F's < 2.00$. Thus, with the exception of prolactin, the marked changes of cell proliferative activity observed prior to this examination seemed to be independent of the variations of endocrine activity. It should underscored, however, that the changes of endocrine activity were relatively small (likely owing the amount of time between the blood sampling and the actual examination). Therefore, as these hormonal measures did not significantly vary between baseline and the academic examination, it is unlikely they reliably predicted the marked changes of immune activity.

Insert Table 30 about here

Predictors of Endocrine/Immune Activity Associated with the Anticipation of the Final Exam: Stressor History & Use of Coping

As with the Introductory Psychology examination, an attempt was made to determine the behavioral correlates of the alterations of endocrine and immune activity prior to both the midterm and the final examination. In contrast to the hormonal measures, several behavioral variables were predictive of the changes of immune activity observed prior to the examination, particularly with respect to the *final* examination period. As before (Experiment 2B), only the Intensity/Severity subscales of the Life Events Scale and the Daily Hassles Scale were used. Moreover, to assess the relationship between subjects' use of coping strategies and the exam-related endocrine/immune changes, only the composite scales including Emotional Expression plus Social Support Seeking, Emotional Containment plus Passivity as well as Individual Coping plus Cognitive Restructuring were used as predictors. Again, regression analyses were conducted independently for subjects who were tested prior to their midterm and subjects who provided a sample prior to their final examination.

Among subjects who were tested prior to the *midterm* examination, it seemed that stressor history, in the form of the Intensity of Major Events neither predicted the changes of the plasma hormones nor the changes of immune activity, $F < 1$. In contrast to Major Life Events, the Severity of Daily Life Hassles predicted the changes of plasma prolactin ($\beta = .54$, $sr^2 = .24$), $F(1, 18) = 5.58$, $p < .05$ (see Table 31). That is, subjects who rated the Daily Life Hassles they encountered as more severe were more likely to exhibit greater elevations of plasma prolactin prior to their midterm examination. Moreover, approximately 24 percent of the variability of the changes of prolactin could be attributed to the severity of hassles these subjects' had to contend with in the previous month. However, other than the changes of prolactin, previous stressor history did not predict the alterations of either plasma ACTH or cortisol or any of the immune measures. These

findings are contrary to the data obtained from subjects tested immediately prior to their Introductory Psychology examination (Experiment 2B). However, it is suggested that inasmuch as the present data were obtained during a different period of the day (afternoon vs. a morning sample reported in Experiment 2B), as well as about 24 hours prior an entire midterm examination period, it seems possible that these factors could have contributed to finding a positive relationship between the severity of hassles and the prolactin changes. Moreover, the present correlations are reported in a small sample size, and thus, may not have been found if we had the opportunity to assess this relationship in a larger sample.

 Insert Table 31 about here

Among the subjects who were tested at baseline and the day prior to their first *final* examination, only the Intensity of Major Life Events seemed to be related to the changes of cell proliferation stimulated by the 0.625 ug concentration of PHA ($\beta = -.50$, $sr^2 = .24$), $F(1, 19) = 6.03$, $p < .05$ (see Table 32). Moreover, as observed in our earlier studies, subjects who reported more Intense Major Life Events (irrespective of their level of depressive symptomatology) were less likely to show the changes of cell proliferation provoked by the anticipation of their final examination. The association between Major Life Events and the changes PHA-stimulated cell proliferation, however, failed to reach statistical significance at the 1.25 and 2.5 ug doses of PHA. Moreover, the Intensity of Major Life Events did not predict the changes of Con A-stimulated cell proliferation (at any single dose of Con A) observed prior to the final examination.

 Insert Table 32 about here

As in the preceding experiment, the relationship(s) between coping profiles and the changes of endocrine and immune activity in anticipation of the midterm or final examination periods were assessed. While subjects' use of coping did not predict the changes of either plasma ACTH, cortisol or prolactin, $F's < 2.00$, the use of specific forms of coping predicted the changes of immune activity prior to both examination sessions. Indeed, subjects who favored the use of Emotional Containment plus Passivity exhibited reduced changes of PHA-stimulated cell proliferation (at all three doses of PHA) prior to their first midterm examination ($\beta's = -.58, -.63$ and $-.85$, $sr^2's = .18, .21$ and $.38$), $F's (1, 22) = 4.98, 5.32$ and 12.11 , $p's < .05$, for the 0.625, 1.25 and 2.5 ug doses of PHA, respectively (see Table 33). Between 18 and 38 percent of the variance of the changes of proliferative activity could be accounted for by subjects' use of Emotional Containment plus Passivity, after the influence of subjects' BDI scores were statistically removed. In contrast to the midterm examination, use of coping was not associated with the changes of cell proliferative activity prior to the final examination, $F's < 2.0$.

 Insert Table 33 about here

In contrast to stressor history or the use of coping strategies, neither the expectancies of academic performance nor the perception of stress associated with the examination (as measured by both the PSS and the Examination Questionnaire) were related to either the endocrine or the immune changes observed at the two examination sessions, $F's < 1$.

Predictors of Endocrine/Immune Activity Associated with the Anticipation of the Final Exam: Stress Perception, Mastery & Quality of Life

In addition to the behavioral measures of subjects' stressor history and use of coping, we also examined whether certain subject characteristics, including basal stress perception (PSS), perception of mastery as well as aspects of Quality of Life might contribute to the interindividual variability of the immune alterations exhibited prior to the first *final* examination. With respect to stress perception, it was noted that the Perceived Stress Scale scores did not change between baseline and the final examination period, $F(1, 22) = .005$, $p > .05$.

The lack of changes of perceived stress over the two sampling sessions is inconsistent with data reported by Armario et al., 1996, and more recently, Maes et al., 1998, who demonstrated that Perceived Stress scores were elevated among medical students prior to their examinations. Inasmuch as the subjects from the preceding and present investigation were first year Carleton University students enrolled in Introductory Psychology, it seems possible that this population is distinct in terms of overall stress perception relative to that observed among medical students.

At this juncture, however, it seems appropriate to note that while stress perception did not change over the two sampling periods (baseline and prior to the final examination), perceived stress did predict the exam-related alterations of cell proliferative activity. In particular, subjects who had greater stress perception exhibited reduced alterations of both Con A and PHA-stimulated cell proliferation prior to their first examination, (r 's = $-.44$, $-.48$ and $-.45$), F 's(1, 18) = 4.42, 5.32 and 4.50, p 's < .05 for the 1.0 and 2.0 ug doses of Con A and the 1.25 ug dose of PHA, respectively. In contrast to cell proliferation, stress perception did not predict the changes of either plasma ACTH, cortisol or prolactin associated with the first examination, F 's < 1.5.

It could be argued that negative association between Perceived Stress scores and the alterations of cell proliferation prior to the final exam was a spurious finding, owing to the small sample size. Alternatively, the relationship between Perceived Stress and the changes of cell proliferation could be attributed to its association with behavioral variables, including Mastery and Life Satisfaction. Indeed, it was observed that both Mastery and Life Satisfaction were negatively correlated with Perceived Stress, (zero-order r 's = $-.71$ and $-.72$), $F(1, 25; 1, 22) = 23.50; 27.95$, p 's $< .0001$. Moreover, as seen below, both of these variables were positively correlated to the cell proliferative measures.

Inasmuch as Mastery and Life Satisfaction were both highly correlated to Perceived Stress, subsequent hierarchical regression analyses were conducted to determine whether several variables, in combination, would maximally predict the changes of immune activity. In these regression analyses, Mastery and Life Satisfaction were entered into the regression equation after BDI scores. These analyses indicated that both Mastery and Life Satisfaction accounted for significant proportions of unique variance of the changes of Con A-stimulated cell proliferation over and above that which could be attributed to depressive symptomatology, (β 's = $.45$, $.63$ and $.69$, sr^2 's = $.14$, $.27$ and $.32$), F 's(1, 20) = 3.29 , 8.83 and 9.77 , p 's = n.s., $.01$, and $.01$, for Mastery (1.0, 2.0 and 5.0 ug Con A doses, respectively), and (β 's = $.81$, $.54$ and $.63$, sr^2 's = $.35$, $.16$ and $.24$), F 's (1, 19) = 10.08 , 6.26 , 9.94 , p 's $< .01$, $.05$, and $.01$ for Life Satisfaction, (1.0, 2.0 and 5.0 doses of Con A, respectively; see Table 34). Thus, between 15 to 36 percent of the variability of the changes of cell proliferative activity were accounted for by the combination of Mastery and Life Satisfaction. Curiously, Mastery alone was the best predictor of the changes of PHA-stimulated lymphocyte proliferation, (r 's = $+.41$, $+.61$, and $+.63$), F 's(1, 21) = 4.44 , 12.72 and 13.63 , p 's $< .05$, $.01$ and $.01$ (for the 0.625, 1.25 and 2.5 ug doses of PHA, respectively, see Table 35). In contrast to cell proliferation, the alterations of neutrophil and macrophage activity were not associated with either

Perceived Stress, Life Satisfaction or Mastery scores, F 's < 1.5 . Thus, it is conceivable that individuals who are satisfied with their lives and have a developed sense of mastery, may be more likely to show the greatest changes of immune activity (as defined by cell proliferative activity) prior to an anticipated environmental challenge. Moreover, as will be detailed within the General Discussion, it is possible that, among a heterogeneous "nondepressed" university student population (like those who are enrolled in Introductory Psychology), the elevation of cell proliferative activity (which is shown to be more exaggerated among satisfied students with a sense of Mastery) may be an index of adaptive changes to impending (and more protracted) types of environmental challenges, such as a final examination period.

 Insert Tables 34 and 35 about here

Experiment 4: Influence of Depressive Subtype on Immune & Neuroendocrine Activity Prior To and Following SSRI Treatment

It will be recalled that individuals with depressive illness display alterations of both enumerative and functional immune parameters (Maes, 1995; O'Leary, 1990; Weisse, 1992). Among major depressives, suppression of various components of the immune response have been reported (e.g., Calabrese, Kling, & Gold, 1987; Evans, et al., 1988; Herbert & Cohen, 1993; Kiecolt-Glaser & Glaser, 1991), including reduced mitogen-stimulated lymphocyte proliferation (e.g., Calabrese, et al., 1987; Cosyns, et al., 1989; Darko, et al., 1986; Kronfol & House, 1984; Levy, Fernstrom, Herberman, et al., 1991; Schleifer, Keller, Meyerson, Raskin, Davis, & Stein, 1984; Syvalahti, Eskola, Ruuskanen, & Laine, 1985), NK cell activity (e.g., Darko, et al., 1991; Maes, et al., 1992; Mohl, Huang, Bowden, & al, 1987). Yet, other investigations have not observed such effects (e.g., Darko, et al., 1989; Darko, et al., 1991; Miller, et al., 1993).

In accounting for the immunosuppression observed among depressed individuals, it was suggested that such an outcome could be secondary to the release of immune products, including cytokines from an activated immune system (Maes, 1995; Maes, et al., 1993; Maes, Bosmans, & Meltzer, 1995; Maes, et al., 1995a, 1995b; Seidel, Arolt, Huntstiger, Rink, Behnisch, & Kirchner, 1996a; Sluzewska et al., 1996). Indeed, it was demonstrated that severe (melancholic) depression was associated with increased mitogen-stimulated IL-1, IL-2, IL-6 (and their receptors), as well as elevated levels of acute phase proteins (Maes et al., 1995a; Maes, et al., 1995b; Seidel, et al., 1996a).

As suggested earlier, in addition to the severity of depression, the chronicity of the illness as well as the presence of typical vs. atypical symptoms, may be important determinants of the immune changes associated with the illness (Ravindran, et al., 1997a; Anisman, et al., 1998). Indeed, it has been reported that the elevations of NK cells observed in dysthymics and major depressives were less evident among atypical depressives (Ravindran, et al., 1995a; Ravindran, et al., 1997a; Ravindran, et al., 1997b), whereas mitogen-stimulated IL-1 β levels were elevated only among dysthymic patients, irrespective of their neurovegetative profiles. Moreover, the magnitude of this elevation was directly related to the duration of illness and inversely related to age of onset (Anisman, et al., 1998; Ravindran, et al., 1997a). Accordingly, one purpose of the present study was to ascertain whether the cell proliferative changes that have been reported in depressed subjects were likewise related to the chronicity of the illness, as well as the neurovegetative characteristics of the depression (i.e., the presence of typical vs. atypical symptoms).

A second purpose of Experiment 4 was to assess whether the immune changes seen in depression are normalized with the alleviation of symptoms. It is curious, that although there have been numerous studies that assessed the immune concomitants of depression, there have been few reports concerning the immune changes that occur with the alleviation of depressive symptoms. In this respect, Irwin et al. (1990b) reported that

the alleviation of symptoms was accompanied by a normalization of NK functioning, while Maes et al. (1997) observed the normalization of some of the cytokine abnormalities. The present investigation evaluated the variations of mitogen-stimulated cell proliferation that accompanied the alleviation of depressive illness following the treatment with selective serotonin reuptake inhibitors (SSRIs). Moreover, where data was available, we assessed whether the change of particular clinical measures, such as the Hamilton Depression Rating Scale predicted the alterations of cell proliferation that might be observed following SSRI treatment.

Subjects

Subjects were obtained by newspaper advertisements or from referrals to the Mood Disorders Clinic (outpatients) at the Royal Ottawa Hospital. A total of 26 patients with major depression, 63 primary dysthymic patients and 17 nondepressed controls participated in the study (age range 25-55 years). The patients satisfied the DSM-III-R/IV criteria for their respective disorders and were free from any other concurrent Axis I or Axis II disorder. Patients with major depression had a primary diagnosis of moderate depression (as defined by the Clinical Global Impressions Scale; CGI). Dysthymic patients met both the criteria for primary dysthymia as well as Akiskal's criteria for subaffective dysthymia (Akiskal, 1990). Additionally, none of the dysthymic patients met the criteria for concurrent major depression.

At the beginning of the study, subjects from both depressive groups were screened by a psychiatrist, who administered the 29-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967) and the Montgomery-Asberg Depression Rating scale (MADRS) (Montgomery & Asberg, 1979). For the drug trials involving the dysthymic patients, psychiatrists also administered the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959) and the Clinical Global Impression Scale (CGI; Guy, 1976). These clinical scales were used to determine the severity of depression and anxiety symptoms, as well as the presence of atypical symptoms. Major depressive patients were considered to have atypical depression

if they fulfilled the Columbia criteria for this illness, namely scoring 4 on the Atypical Depression Diagnostic Scale (ADDS). Further, both major depressive and dysthymic patients were classified as having atypical features if the sum of their scores on the HAM-D items #23-28 was greater than 6. Thus, the present investigation included controls ($n = 17$), typical major depressives ($n = 10$), atypical major depressives ($n = 16$), atypical dysthymics ($n = 31$), and typical dysthymics ($n = 32$).

The control subjects, who were blue- or white-collar hospital and university employees, as well as mature university students (> 25 years of age), were obtained through advertisements within the Royal Ottawa Hospital, Carleton University and the University of Ottawa. These volunteers were screened using the clinician-rated Mini-International Neuropsychiatric Interview (M.I.N.I.) to exclude any past or present DSM-III-R/IV Axis I disorders (Sheehan, Lecrubier, Janavs, Knapp, Weiller, Sheehan, et al., 1992). As well, these subjects had a BDI score of less than 4 and scored 0 on the first item ("I do not feel sad") (Beck, Ward, 1961).

As in Experiment 1A, exclusion criteria for all subjects included any viral illness in the preceding 2 weeks, as well as any illness/medical condition which could influence HPA or immune activity, including severe allergies, hypertension, recurrent dermatitis, as well as any malignant, hematologic, endocrine, pulmonary, cardiovascular, renal hepatic, gastrointestinal or neurological disease. Further, pregnant or lactating women were excluded. Control subjects were excluded if they were taking any prescribed physical (e.g., antibiotics) or psychotropic medication. Subjects in all groups reported alcohol consumption of less than 3.0 drinks/week and less than 3.0 cups/day of caffeinated beverages. The amount of cigarette smoking was documented and, none of the subjects reported substance abuse.

Procedures

During the screening visit, data were collected on the characteristics of the current episode (for the depressed groups), past medical/psychiatric history as well as family history of psychiatric illness. All subjects underwent a full physical examination as well as a clinical evaluation, which included full blood counts, urinalysis and an EKG. As mentioned previously, subjects from the depressed groups had several standardized clinical measures performed, including the HAM-D, MADRS, and the CGI.

Following the initial diagnostic interview and informed consent being obtained, all depressed patients underwent a drug wash-out period of at least one week. Those patients who were being treated with medication at the time of the study underwent a further wash-out period which was 5 times the length of the half-life of the medication in question. (for instance, patients on fluoxetine at the time of the investigation underwent a 5-week washout). Following the wash-out period, all depressed patients were randomly assigned to be treated with either fluoxetine, paroxetine, sertraline, venlafaxine, or placebo.

As subjects were obtained from several clinical trials, some differences in the treatment procedures were inevitable. The sertraline and paroxetine patients were obtained from double-blind placebo-controlled studies, whereas the venlafaxine subjects were obtained from an open-label trial. Thus, in the present investigation, no attempt was made to compare between drug treatments or study conditions. Rather, the primary purpose of Experiment 4 was to determine whether immune normalization was observed in those patients who exhibited a positive treatment response vs. those who did not experience illness alleviation.

All blood-taking procedures were conducted at the Mood Disorders Clinic at the Royal Ottawa Hospital. Similar to sampling procedures outlined in Experiment 1A, on the baseline test day, between 0800-1000h, subjects had a catheter inserted into the antecubital fossa of their non-dominant arm. All subjects were asked to watch a neutral videotape for a

period of 30 minutes. Blood was automatically withdrawn using a Dakmed ambulatory pump at the time of needle insertion and 30 minutes thereafter. These procedures were repeated following 12 weeks of antidepressant (or placebo) treatment. Control subjects had blood taken at similar time intervals.

In the present study, both Con A and PHA-stimulated lymphocyte proliferation were assessed at baseline and following treatment. Additionally, baseline macrophage and neutrophil activity was examined among a portion of depressed patients who began treatment when chemiluminescence procedures were available to our laboratory.

Statistical Analyses: In order to compare the functional immune activity of all depressive subgroups with the control subjects, both the major depressives and the dysthymic subjects were subcategorized according to the presence of typical vs. atypical symptomatology (i.e., presence of atypical symptomatology was not a separate between-groups variable). Therefore, baseline cell proliferative measures were analyzed using 5 (Group) x Dose of Mitogen (Con A or PHA doses) analyses of variance with repeated measures. To assess whether 12 weeks of SSRI treatment influenced the immune activity among the patient groups, separate 2 (Group; MDD vs. Dysthymia) x 2 (Treatment; SSRI vs. Placebo) x 2 (Baseline vs. Week 12) x 3 (Dose of Mitogen) analyses of variance with repeated measures were conducted for both Con A and PHA-stimulated cell proliferation. Bonferroni corrections were again used to achieve more conservative α -levels.

Results and Discussion

Demographic and Clinical Efficacy Measures Prior to Treatment

Table 36 show the mean age (years) for the control and each of the patient groups. Mean ages were equivalent across all groups. Atypical groups tended to have a greater female to male ratio.

Insert Table 36 about here

Furthermore, Table 37 shows the mean total scores on the HAM-D (17-item) and the MADRS scales for all major depressive and dysthymic subjects prior to treatment. As well, mean baseline CGI and HAM-A scores are shown for the dysthymic groups.

 Insert Table 37 about here

Basal Functional Immune Activity

The analyses of variance revealed that, prior to treatment, cell proliferation in the $[H]^3$ thymidine uptake assay (as measured by $[H]^3$ c.p.m) varied as a function of the Depressive Subtype x Dose of Mitogen interactions, F 's(8, 234; 8, 216) = 2.66 and 4.88, p 's < .01 for both Con A- and PHA-stimulated cell proliferation, respectively. Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple effects comprising these interactions indicated that both the dysthymic subgroups (i.e., typical or atypical) exhibited reduced T-cell proliferation at all of the Con A and PHA doses relative to the control and the major depressive groups. In general, neither of the depressive subtypes could be distinguished on the basis of typical vs. atypical symptomatology. Relative to the atypical major depressives, modest decline (about 25 percent) of 5.0 ug Con A-stimulated cell proliferation was exhibited among individual with typical major depression. Moreover, the typical major depressives showed attenuated Con A-stimulated (but not PHA-stimulated) cell proliferation (reductions of about 40 percent) relative to the control group ($\alpha = .05$; see Figure 21), the proliferation among atypical major depressive patients did not differ from control values.

 Insert Figure 21 about here

As mentioned earlier, baseline macrophage and neutrophil activity were also assessed among control, major depressive and dysthymic subjects (see Figure 22). Prior

to treatment, these groups did not vary with respect to peak PMA-stimulated macrophage or neutrophil activity, F 's < 1 . Moreover, the mean time to reach the peak neutrophil activity did not vary between these groups, $F < 1$. Thus, these data indicate that variations of baseline macrophage or neutrophil activity did not vary as a function of affective illness, regardless of either the chronicity vs. severity of depression (at least within the 12 week treatment period) or the presence of atypical vs. typical features.

Functional Immune Activity Following Antidepressant Treatment

Cell proliferative data were obtained from a subset of dysthymic, as well as a smaller number of MDD subjects, who had participated in clinical trials at the Mood Disorders Clinic at the Royal Ottawa Hospital. For the purpose of the present investigation, comparisons of the mitogen-stimulated cell proliferation as well as macrophage and neutrophil activity following 12 weeks of either SSRI treatment vs. placebo were made. For the reader's interest, the changes of the baseline HAM-D and MADRS scores are shown for the dysthymic groups. Unfortunately, there were not enough MDD placebo subjects completing treatment. Thus, the data from the MDD are not shown (see Table 38).

 Insert Table 38 about here

It will be recalled that sertraline and paroxetine-treated patients were obtained from double-blind placebo-controlled studies. Subjects treated with venlafaxine were obtained from an open-label trial. Inasmuch as our interest was to assess whether immune normalization would occur among patients who exhibited a positive treatment response (vs. those who did not demonstrate significant alleviation of illness), no attempt was made to compare between drug treatments or study conditions.

The analyses of variance of revealed that in this subset of dysthymics patients, cell proliferation was reduced relative to major depressive patients (as observed in the

entire data set). However, neither Con A nor PHA-stimulated cell proliferation varied as a function of either the Treatment or the Depressive Subtype x Treatment interactions, F 's < 1 (see Figure 22; only dysthymic subjects' data shown).

 Insert Figure 22 about here

A potentially more important comparison would be to assess cell proliferation among the treatment “responders” vs. “nonresponders” for the different illness subtypes. Unfortunately, there were few MDD placebo subjects who completed the 12 week treatment regimen, and dividing these into responders and nonresponders would have yielded too few subjects for the analyses of variance. Accordingly, a separate 2 (Treatment; SSRI vs. Placebo) x 2 (Treatment Response; Responders vs. Nonresponders) x 3 (Dose of Mitogen) analyses of variance with repeated measures was conducted of the dysthymics who completed the 12 week regimen. The SSRI- and placebo-treated dysthymic subjects were categorized on the basis of their response to treatment. Responders were defined as those subjects who showed both a 50% decline of their 17-item HAM-D scores (relative to baseline) and scored lower than 10. Nonresponders were subjects who did not meet this criteria following the 12 week treatment period.

The analysis of variance indicated that neither the Con A nor PHA-stimulated cell proliferation varied as a function of Drug, Treatment Response or any of the interactions involving these two variables, F 's < 1 . Thus, the marked reduction of cell proliferative activity observed among dysthymic patients at baseline was not modified by SSRI treatment (at least, not within the limits of the treatment period of the present investigation). However, it is conceivable that, as reported by Ravindran et al. (1995b) concerning circulating NK cells, the normalization of immune activity which *might* occur following SSRI treatment may require a relatively long period of treatment (e.g., 6 months).

At this juncture, it would be interesting to determine the effects of pharmacotherapy on the functional immune parameters among the MDD subjects. However, as indicated earlier, there were few placebo subjects within this depressive subgroup who completed treatment. Moreover, there were few who did *not* respond to the SSRI treatment. Thus, an appropriate analysis of the variability of functional immune activity of the Responders and Nonresponders within this depressive subgroup was not conducted. It was notable that among the SSRI-treated MDD subjects who responded to treatment, PHA-stimulated cell proliferation varied as a function of the (Sampling Period; Baseline vs. Week 12) x (Dose of Mitogen) interaction, $F(2, 16) = 10.65$, $p < .001$. Surprisingly, Newman-Keuls multiple comparisons of the simple effects comprising this interaction indicated that cell proliferation of the lymphocytes stimulated with 1.25 and 2.5 ug of PHA *declined* from Baseline to Week 12. Indeed, at the 2.5 ug dose of PHA, cell proliferation was approximately 50 percent of the Baseline values. The proliferative activity of lymphocytes stimulated by Con A was also found to vary as a function of the Sampling Period, $F(2, 16) = 16.09$, $p < .01$, indicating that cell proliferation among drug responders decreased over the 12 weeks of treatment. While these observations are provisional (i.e., demonstrated in 9 MDD subjects who responded to SSRI treatment), they were consistent for both of the mitogens used and were exhibited across all but the lowest dose of PHA. Interestingly, among the dysthymic patients who responded to the SSRI treatment, a trend for a main effect of Sampling Period was observed, $F(1, 17) = 2.87$, $p = .10$, for cell proliferation. Overall, an 35% *increase* of Con A-stimulated cell proliferation (across all the Con A doses) was observed following successful SSRI treatment. However, this trend was not observed among the lymphocyte cultures stimulated with PHA (see Figure 23).

These data indicate that while some functional immune components are not readily modifiable by SSRI treatment at least within 12 weeks of treatment. However, inasmuch as there is a trend for an increase of Con A-stimulated cell proliferation among

dysthymic treatment responders (and a decrease of this immune measure among major depressive drug responders), it would be useful to examine whether such an effect might be more pronounced with sustained pharmacotherapy over a longer treatment period.

Although the findings concerning the Con A-stimulated cell proliferation among the dysthymic treatment responders is promising, there is limited power to detect a statistically significant effect owing to the small number of subjects as well as a modest effect size ($\eta^2 = 0.22$). Further, owing to the small number of subjects it was not possible to assess the source (i.e., response to treatment, direct effect of the drug) for these immune changes over the treatment period.

 Insert Figure 23 about here

Clinical Correlates of Functional Immune Activity

To determine whether any alterations of depressive symptomatology and/or illness characteristics were predictive of functional immune changes, simple regression analyses were conducted using the age of onset, the degree of atypical features present (i.e., clinicians' ratings of the HAM-D atypical items #23-28) as well as the absolute change of the HAM-D (17-item), MADRS and CGI scores (i.e., the difference between Week 12 and Baseline) as predictors. These regressions were performed to determine if any of these clinical treatment variables would predict the changes of the Con A and PHA-stimulated cell proliferation. As there were an insufficient number of major depressives, these regression analyses only included the dysthymic subjects.

These regression analyses revealed that neither the age of onset, the degree of atypical symptomatology nor any of the changes in the clinical measures (i.e., HAM-D, MADRAS or HAM-A) were predictive of alterations of immune activity following the treatment period, F 's < 1. These findings are not surprising given that overall, dysthymic

subjects did not show significant alterations of cell proliferation following the SSRI treatment.

General Discussion

The present investigation was conducted to determine whether alterations of endocrine and immune functioning would be engendered by environmental challenges, and to identify some of the factors which might contribute in this respect. In particular, we examined whether alterations of endocrine and/or immune activity among nondepressed subjects would be (a) observed following exposure to either simple or complex cognitive laboratory challenges, (b) affected by a naturalistic stressor (i.e., the anticipation of an academic examination or set of examinations) and, (c) influenced by subjects' behavioral profiles (e.g., depressive symptomatology, stressor history, use of coping strategies, as well as Quality of Life indices) during basal and stressful conditions. Furthermore, this investigation also assessed whether (d) depressive illness was associated with functional immune alterations, (e) these varied with the specific characteristics of the illness (i.e., presence of typical vs. atypical symptomatology) and, (f) these were evident in dysthymia, as previously reported in acute major depressive disorder, and finally, (g) the alterations of functional immune activity would be normalized following 12 weeks of SSRI treatment.

Behavioral Correlates of Basal Endocrine, Sympathetic & Immune Activity

Prior to assessing endocrine and immune activity associated with the stress of either the laboratory challenges or an academic examination, basal levels of these biological substrates were assessed in relation to the behavioral indices. It was notable that 18 percent of the 174 subjects who donated a baseline blood sample had significant levels of depressive symptoms, as measured by the Beck Depression Inventory. This number appears to be high, but is consistent with that reported by Wong and Whitaker (1994) using a university population. The source for the high degree of depressive symptomatology cannot be deduced with absolute certainty. However, as the

advertisement for subjects specified that the study was aimed at identifying the effects of life events and mood states on endocrine and immune activity measured from blood samples, this may have been particularly attractive to those students who had been encountering depressive symptoms. Moreover, a recent report examining symptoms of the stress among first year university students indicated that feelings of anxiety and depression were frequent (Arthur, 1998; Rocha & Ortigasoto, 1995). Furthermore, stress perception and depression tended to increase during the course of the academic year (Arthur, 1998). Thus, it is conceivable that in addition to the influence of the advertisement used to obtain subjects in the present report, there was a significant chance of encountering students with pronounced feelings of depression, particularly as the academic year progressed.

It is important, however, at this juncture to state that in the present investigation, the BDI was not used as a diagnostic tool, it was simply utilized as a screening device. As mentioned earlier, we used the students' BDI scores for arbitrary subgrouping based upon classification criteria reported by Beck & Beck, 1972. These authors, for instance, suggested that a total average score of 9.37 on the 13-item Beck Depression Inventory was highly correlated with clinicians' ratings of "mild clinical depression" within a sample of 600 subjects. Furthermore, while the 21-item version of this self-report depression scale was redesigned as clinical diagnostic tool (i.e., the 13-item shortened scale form was designed for family physicians as a diagnostic screening tool; see Beck & Beck, 1972), it should always be used as one of several clinical measures such as an in-depth evaluation of patients' medical history and/or other clinical depression measures (e.g., HAM-D) to confirm diagnosis. In fact, in the final experiment of this thesis, several clinical efficacy measures were used, including the HAM-D, HAM-A, CGI and MADRS scales. Although the use of these clinical efficacy measures among the university students may have given us a more in-depth profile of subjects' depressive symptomatology, their use in the student sample of the present investigation would have been impractical.

Additionally, experiments previously conducted in our laboratory showed that BDI scores were highly correlated to both HAM-D and MADRS scores among approximately 100 dysthymic patients, a finding consistent with those observed among a mixed community population (Beck & Beck, 1972). Finally, unlike other self-report symptomatology scales (including the MMPI, the Multiple Affect Adjective Checklist or even the Zung Self-Rating Depression Scale), the BDI better discriminated between depressive and anxiety symptoms (see Beck & Beck, 1972). Thus, due to our study objectives and issues of practicality, we used the BDI for classifying the university students into subgroups based on their perception of their depressive symptoms. It is notable (and interesting for future investigations) that subjects in the "High" BDI subgroup, did, in fact, have stressor history and coping profiles similar to those observed among dysthymic outpatients (see below). It would, nonetheless, be inappropriate to suggest that this particular group of subjects could be further classified or diagnosed as dysthymic.

It is curious, however, that the average level of depressive symptomatology of subjects within the High BDI group (defined as > 9) as well as their stressor history and coping profiles were comparable to that observed among dysthymic outpatients (Ravindran et al, 1995c). These data indicate that similar to mild, but chronically depressed individuals (i.e., those who have dysthymic illness) persons with subclinical levels of depression symptoms present with similar stress-related behavioral profiles. Although the implications of these data are not known, it is tentatively suggested that subjects with High BDI scores might have greater risk of developing more *clinically* severe (and/or chronic) levels of depressive symptomatology simply from having a more marked stress-related behavioral profile. Of course, this supposition is speculative and may only be confirmed using prospective methodology.

Of particular interest was the finding that the number and intensity of positive events did not vary as a function of BDI scores. This contrasts with *clinically* depressed

individuals who reported fewer uplifts and also perceived these uplifts as being less rewarding than did nondepressed controls (Beckham & Adams, 1984; Brown & Harris, 1989; Kanner et al., 1981; Ravindran et al., 1995b; Ravindran et al., 1997). It is conceivable that the perception of daily uplifts may be a sensitive behavioral measure for distinguishing between subclinical vs. mild clinical depression or dysthymia. In fact, the presence of unusually low levels of uplifts may be an important predictor of relapse among treated major depressive patients, as well as being a characteristic feature of dysthymic individuals (Ravindran et al., 1998a). Of course, the present findings with respect to daily uplifts were obtained in a younger, university population who may have had many sources of uplifts not ordinarily found among mildly depressed or dysthymic subjects. It would be of clinical interest to ascertain whether university students who are dealing with or have dealt with depressive illness report differences with respect to perception of uplifts relative to students who exhibit subclinical or minimal levels of depressive symptomatology.

In addition to the stress-related variables, the High BDI subgroup of the present investigation also showed patterns of coping similar to those previously reported among dysthymic outpatients (Ravindran et al., 1995b; 1996b). Compared to individuals with Low BDI scores, these subjects tended to favor Emotional Expression plus Social Support Seeking, as well as Emotional Containment plus Passivity. In contrast, the groups of the present investigation could not be distinguished from one another with respect to the use of Individual Coping plus Cognitive Restructuring, a finding similarly observed between dysthymic patients and controls. These findings are consistent with those reported by Arthur (1998) who showed that relative to nondepressed students, those with greater levels of depression and/or emotional distress were more likely to favor disengagement coping strategies (i.e., behaviors which allow an individual to avoid or be emotionally distance from stressful stimuli) but did not differ with respect to their use of problem-focused coping.

Subjects who reported more intense depressive symptoms also showed reduced Quality of Life with respect to overall General Health, Health Perception, Energy and Concentration. As well, reduced Alertness, quality of Social Interaction, and Life Satisfaction were also found among subjects with either Moderate or High BDI scores, as was previously observed among dysthymic outpatients (Ravindran et al., 1998a, 1998b). Clearly, the patterns of the stress-related behavioral measures, coping styles, as well as quality of life indices among individuals who display significant depressive symptomatology or depressive "temperment" (but who are not clinically depressed), are distinguishable from those of nondepressed individuals. Whether these characteristics of depressive temperment predispose an individual to either dysthymia or MDD has been a topic of some interest (see Akiskal, 1989; Klein, 1990; Phillips, Gunderson, Hirschfeld & Smith, 1990), and, it would be of considerable value to ascertain the academic and psychosocial consequences of these characteristics in a university population. It is notable that although dysfunctional attitudes, adverse life events and low self-esteem predicted current levels of depressive symptomatology within a college population, the best predictor of future depression (i.e., after three months) was the baseline level of depressive symptoms (Wong & Whitaker, 1994). Thus, at this juncture it would be interesting to assess whether considerable (but subclinical) levels of depression (i.e., like that observed among the High BDI group within the present investigation) would remain stable over a longer period, and whether these characteristics would be associated with adverse academic consequences.

In addition to basal levels of depressive symptomatology, we assessed the relationships between the stress-related variables (i.e., stressor history, coping profiles) as well as Quality of Life, and the basal endocrine and immune measures. At baseline, the frequency and severity of daily hassles were negatively associated with basal ACTH concentrations. However, neither daily hassles nor major life events predicted basal levels of other HPA hormones (cortisol and prolactin), sympathetic neurochemical

activity (as reflected by plasma NE and Epi) or levels of immune functioning (mitogen-stimulated T-cell proliferation as well as macrophage and neutrophil activity). Thus, during nonstressful conditions, basal endocrine and immune activity among nondepressed individuals could not be attributed to either day-to-day minor annoyances or the major life events they had encountered. Of course, the biological measures were only determined at a single time point and, it is certainly possible that alternative evaluation procedures (i.e., multiple saliva sampling) may have been more informative in deducing or reflecting the cumulative effects of the recent life stressors encountered.

Although the hormonal and immune measures used in the present investigation were not related to life stressors, this does not necessarily preclude health-related consequences. Moreover, it is possible that certain life stressors (i.e., minor daily annoyances) may be more important in determining health-related outcomes. Indeed, investigations which used self-reported somatic and psychological symptomatology as criterion measures found that daily life hassles had a more profound impact on these reported symptoms than did major life events (e.g., see Ruffin, 1993; Nakano, 1993). Furthermore, it seemed that daily hassles alone, irrespective of the coping strategies used to deal with these hassles, were predictive of minor physical ailments (Kohn, Hay, & Legere, 1994). Thus, it would be of interest at this juncture to determine whether perceived hassles and illness symptoms were related to basal hormonal, sympathetic and/or immune activity.

It is well known that stressful events influence immune functioning (see Anisman et al., 1993; Blalock, 1994; Calabrese et al., 1987; Clover et al., 1989; Cohen & Herbert, 1996; Cohen & Williamson, 1991; Delahanty et al., 1997; Dunn, 1995; Ironson et al., 1997; Stone et al., 1992; Weiss et al., 1996), affect cortisol secretion (a hallmark of stressful experiences), and may elicit immunosuppressive reactions (Munck et al., 1984; McEwen, 1995). However, in the present investigation basal cortisol concentrations were, unexpectedly, found to be *positively* related to the proliferative activity of lymphocytes.

This finding is, of course, contrary to the dogma regarding the immunosuppressive effects of stressors. However, it has been previously shown that mild stressful events may actually give rise to elevations of immune activity (Croiset et al., 1987; Lysle, Cunnick & Rabin, 1990). Thus, modest increases of cortisol and mitogen-stimulated cell proliferative activity may be reflective of the relatively mild day-to-day stressors that are often encountered. Moreover, the action of *modest* increases of cortisol may not be one of suppressing immune functioning. Instead, cortisol may act to limit excessive immune activity in response to stressors, thus acting against potential autoimmune responses that might otherwise be provoked (Munck et al., 1984).

While individuals' stressor history and basal hormonal activity may impact on immune functioning (and potentially, health outcome), it is important to evaluate the coping styles normally used to deal with environmental challenges. As alluded to earlier, persons may differ with respect to coping strategies they use in response to daily stressors. Thus, other things being equal, individuals may exhibit differential adverse effects depending upon the coping strategies they adopt in the face of these challenges. For instance, it has been suggested that while cognitive restructuring is a more appropriate coping style, emotion-focused coping may be less adaptive in the face of controllable stressors (see Aldwin, 1994; Lazarus, 1993). Further, it was posited that the excessive use of emotion-focused coping among depressed patients may have favored their inability to deal with environmental and social demands, hence limiting their recovery (Ravindran et al., 1995b; Anisman, Ravindran, Griffiths & Merali, 1998). Of course, the effectiveness of a given coping style will be situation- and individual-specific (Aldwin, 1994). In the present investigation, it was of interest that coping profiles were predictive of basal immune activity. In particular, subjects who favored Emotional Expression plus Social Support Seeking were more likely to exhibit greater basal lymphocyte proliferation, an effect which seems to parallel the patterns of immune activity observed in response to mild stressors in animal studies (Croiset et al., 1987;

Fujiwara & Orita, 1987; Weiss, Sundar, Becker & Cierpial, 1989). Interestingly, however, when the variability of these immune measures that could be attributed to basal cortisol was statistically removed, the predictive ability of Emotional Expression plus Social Support Seeking was diminished, and only the use of Individual Coping plus Cognitive Restructuring predicted basal immune activity. These findings suggest that in order to best predict functional immune activity among university students during relatively nonstressful periods, it may be profitable to consider both basal cortisol concentrations and subjects' use of Individual Coping plus Cognitive Restructuring. However, when examining these relationships between coping and these basal immune parameters, daily life hassles should be measured, as in some cases the predictive abilities of coping profiles may be secondary to stressor history.

In addition to coping profiles, two Quality of Life variables, namely Life Satisfaction and physical Energy were associated with basal endocrine and immune activity. In particular, Life Satisfaction was negatively correlated with basal cortisol and prolactin concentrations as well as the proliferative activity of lymphocytes stimulated with Con A. Conversely, physical Energy was positively associated with basal neutrophil activity and PHA-stimulated lymphocyte proliferation. It is noteworthy that these Quality of Life indices were associated with basal biological measures in the present report since it was suggested Quality of Life may be a meaningful index of the residual aspects of depressive illness (Ravindran et al., 1998b). Moreover, as will be discussed shortly, Life Satisfaction was also highly correlated with the changes of immune activity associated with the anticipation of a poignant naturalistic stressor among university students (namely academic examinations). Thus, it is conceivable that to some degree, perceived Quality of Life could impact on hormonal and/or immunological processes, which, in turn, could have implications for the development or the exacerbation of depressive symptomatology.

Influence of Laboratory Challenges on Endocrine & Immune Activity

In general, subjects who were exposed to either the simple laboratory challenge (i.e., the Arithmetic task or the Interview) or the complex challenge (Arithmetic plus a Speech about a neutral topic vs. a Speech of an emotionally-laden topic) did not exhibit significant alterations of either endocrine or immune activity. In fact, each group of subjects (including the controls) exhibited declines of circulating ACTH, cortisol, prolactin over the course of the laboratory session. Moreover, plasma levels of epinephrine did not change following the simple laboratory challenge and declined following both of the more complex challenges. As mentioned earlier, these findings are generally consistent with previous data collected from our laboratory (Griffiths et al., 1997; Ravindran et al., 1996b). However, other studies which used more poignant complex laboratory stressors demonstrated elevations of plasma cortisol, ACTH as well as NE and Epi (e.g., Kirschbaum et al., 1993; Schedlowski et al., 1993; 1996). Thus, it is conceivable that the types of challenges used in the present investigation may not have been sufficiently severe to engender alterations of endocrine or sympathetic activity.

In addition to stressor severity, it is conceivable that particular types of laboratory challenges (such as those which incorporate a *socially* stressful component) and/or challenges which are salient or meaningful for the target population, are more likely to engender alterations of endocrine and/or immune activity. Indeed, immediately following the Interview challenge, 8 of 10 subjects showed elevations of plasma NE, without concomitant changes of immune activity or other plasma hormones. Although these findings are not consistent with those of Griffiths et al. (1997), catecholamine alterations have been observed without changes of HPA-related hormonal activity (Henry, 1993). This occurs particularly when the challenge provokes behavioral or emotional excitation, but is not appraised as being stressful (Henry, 1993). The present findings are consistent with this supposition, and suggest that the social component of a challenge may be an

important factor for eliciting catecholamine variations. Moreover, as discussed earlier, stressors involving a social component may also give rise to changes of HPA-related hormones (e.g., Kirschbaum et al., 1993), indicating that psychosocial stressor effects are not limited to catecholamine alterations.

As mentioned earlier, the nature of the changes of endocrine and/or immune activity in response to a laboratory challenge are likely influenced by the relevance or meaning of the stressor for the target population examined. Indeed, among depressed individuals (see Griffiths et al., 1997; Ravindran et al., 1996b) neither an arithmetic challenge nor a clinical interview concerning either day-to-day positive or negative events provoked significant elevations of plasma cortisol, ACTH or NE (although it will be recalled that both of these laboratory stressors were sufficient to provoke an appreciable increase of circulating NK cells). However, exposure to a mild, but more meaningful (and perhaps stressful) task among depressed individuals (i.e., filling out a questionnaire concerning daily *uplifts*, which has been proposed to be stressful among depressed individuals who are less likely to experience uplifts) was sufficient to provoke changes of circulating NK cells. Thus, in the present investigation, the lack of ACTH, cortisol, prolactin and immune activity changes may have been related to the mild nature of the challenges, as well as the limited meaningfulness of these challenges to subjects.

In addition to these factors, the limited effects of the laboratory challenges may have been related to the nature of the testing procedures. In the present investigation, blood was taken from subjects who had reported to the laboratory relatively early in the morning. This methodological aspect could be important for accounting for the present data as it was recently reported that free salivary cortisol concentrations typically increased by 50 to 75 percent within 30 minutes of awakening, and these findings were stable over several days (Pruessner, et al., 1997). It was proposed that this increase of adrenocortical activity could be part of a central biological mechanism designed to prepare the organism for impending demands (Pruessner et al., 1997). In effect, it is

conceivable that these elevations of cortisol (and potentially other HPA-related hormones) observed following awakening, might be affected by individuals' anticipation of daily events (e.g., appointments, workload etc.). Thus, when the initial sample is taken within 1-2 hours after awakening and, particularly when this is done in an anxiety-provoking situation (i.e., blood being taken in a laboratory setting), basal cortisol levels may be elevated, hence obfuscating any effects attributable to an experimental stressor. According to this position, the apparent lack of challenge-induced elevations of plasma cortisol (and potentially, ACTH and prolactin) may have been secondary to the increases of circulating hormones present even prior to subjects' appointments. Indeed, in both of our laboratory challenge studies, levels of cortisol, ACTH, prolactin (both experiments) and epinephrine (the complex challenge study) declined over the laboratory sampling period. The finding that the greatest concentrations of these hormones were observed shortly after needle insertion is consistent with the view that the routine associated with the experiment may have been perceived as stressful (i.e., the "white coat phenomenon"). It is possible that the elevated cortisol associated with the initial experimental procedures may have acted to inhibit further cortisol release upon exposure to the laboratory stressor (i.e., via negative feedback mechanisms).

At this juncture, it is reasonable to suggest that while the use of blood sampling is an effective way of evaluating functional immune changes associated with environmental challenges, its use in hormone determinations may be problematic. Given that the needle insertion (as well as other cues of the laboratory session) could have been perceived as stressful, the use of multiple saliva samples may have been more appropriate. This method of sampling is much less invasive and is thought to be an accurate index of free cortisol concentration (however, cell proliferative measures could not have been obtained; Kirschbaum & Hellhammer, 1994). Additionally, the use of salivary sampling would have allowed the dynamic variations of several hormones to be simultaneously measured, and would have permitted the assessment of individual differences of

endocrine alterations associated with anticipated challenges. In this respect, it was recently reported that cortisol “responders” (i.e., individuals who exhibited significant cortisol elevations in response to a laboratory challenge) showed different patterns of cortisol activity prior to the laboratory task, relative to “nonresponders” (Lupien et al., 1997). While responders exhibited elevations of cortisol 60 minutes prior to an anticipated memory task, nonresponders showed these elevations 25 minutes before the task. With these issues in mind, it is possible that within the present investigation a longer waiting period (between the needle insertion and the relaxation baseline) would have been advantageous for the assessment of potential hormonal (and immune) alterations that might be associated with the laboratory challenges.

In addition to the assessment of dynamic hormonal changes that might be associated with laboratory stressors, salivary sampling would have allowed the assessment of the relationships between patterns of hormonal activity and health-related variables, such as symptom reporting. For instance, Smyth et al. (1997) recently identified three main subgroups with respect to diurnal variations of endocrine activity; those with a “normal cycle” (subjects who showed the expected reduction of salivary cortisol from peak morning values), those with a “flat” cycle (who showed approximately the same concentrations of salivary cortisol over the course of a 24 hour period), and finally, subjects with an “inconsistent cycle”. Interestingly, individuals with a flat hormonal cycle reported fewer upper respiratory symptoms. In this respect, it would be interesting to determine whether these individuals might also display distinct patterns of hormonal activity prior to or following a salient laboratory challenge.

Finally, it is important to emphasize that considerable interindividual variability exists with respect to both basal and stressor-provoked hormonal levels (e.g., see Lupien et al., 1996; Pruessner et al., 1997; Smyth et al., 1997; Spangler, 1997; Zorrilla, DeRubeis, & Redei, 1995). No doubt, a large number of variables contribute to this diversity, but it is reasonable to suggest that at least some of the variability of endocrine

and immune responses to laboratory or naturalistic challenges may be related to individuals' stressor history, coping profiles and levels of depressive symptomatology (e.g., Pike et al., 1997; Pruessner, Gaab, Hellhammer et al., 1997; Pruessner et al., 1997; Zorrilla, Redei, & DeRubeis, 1994). However, as the number of subjects tested for each of the challenges of the present investigation was relatively small, statistical analyses could not be conducted to identify the contribution of stress/coping factors to the variability of these biological measures. Nevertheless, as will be discussed shortly, these behavioral indices may be important determinants of the endocrine and immune reactivity to naturalistic environmental challenges (namely, academic examinations).

Endocrine & Immune Alterations Associated with an Impending Academic Examination

In contrast to the laboratory challenges, moderate endocrine alterations were associated with the anticipation of the Introductory Psychology examination. Increases of circulating ACTH, prolactin, NE and epinephrine (approximately 25-35 percent) were exhibited within the 1 hour period prior to the Introductory Psychology examination. Curiously, while cortisol is often taken as the prototypical "stress hormone", no significant changes of cortisol were observed, irrespective of whether blood was sampled 1 hour or 24 hours prior to the examination. It seems possible, at least with respect to cortisol, that the stress of an impending Introductory Psychology examination or an impending period of examinations (such as midterms or finals) was not sufficiently severe to engender changes of this hormone. Yet, in earlier studies conducted in this laboratory, elevations of cortisol levels were apparent in anticipation of an academic examination (Griffiths et al., 1997). Likewise, we recently observed that significant elevations of cortisol were exhibited among graduate students (especially among women) immediately prior to an oral thesis defense (an obviously more intense stressor than that used in the present investigation; Lacey, Zaharia, Ravindran, Merali & Anisman, 1998, unpublished data). Thus, the absence of an effect of an academic examination on cortisol concentrations in the present investigation was surprising. Yet, the present findings are

not alone in indicating that stressors, such as examinations, do not necessarily lead to notable cortisol variations (see Armario et al., 1996; Dorian et al., 1982; Glaser, et al., 1994; Spangler, 1997).

In order to account for the lack of cortisol changes across the three experiments of the present investigation, several issues need to be considered. First, cortisol release occurs in pulses within a short period of time, and the hormonal variations that occur in response to stressors persist for relatively brief durations. For instance, the cortisol variations induced by laboratory stressors are thought to occur within approximately 10-15 minutes of stressor presentation and persist for about 30-60 minutes. As such, single stick sampling may not provide an unambiguous gauge of the stress-related pulses or the dynamic (i.e., time course) changes of this hormone. Second, there are considerable interindividual differences of hormonal (and behavioral) reactivity to impending events. These differences may affect either the magnitude and/or the time course of the cortisol (and potentially, other hormonal) responses to environmental stimulation (see Lupien et al., 1997; Pike et al., 1997; Smyth et al., 1997; Spangler, 1997). While some individuals may show large increases of HPA-related hormonal activity in anticipation of environmental challenges, others may exhibit no change or even decreases of circulating cortisol. Moreover, the time course of cortisol variations associated with impending challenges vary appreciably across subjects due to a number of factors, including the perceived stress or anxiety associated with the impending event (e.g., see Deinzer, Kirschbaum, Gresele & Hellhammer, 1997) as well as feelings of mastery (Fenz, 1988) that may develop following the experience with similar events (e.g., see Deinzer, Kirschbaum, Gresele & Hellhammer, 1997; Fenz, 1988; Schedlowski, Wichert, Wagner, & Tewes, 1992).

Of course, the simple exposure to cues associated with the blood sampling procedures (e.g., needle insertion and the "white-coat" phenomena) may contribute to the individual variability of hormonal responses associated with stressor exposure. As

discussed earlier with respect to the laboratory challenges, these methodological issues would have been addressed more effectively by the use of a noninvasive salivary collection technique (Kirschbaum & Hellhammer, 1994). Moreover, collection of multiple salivary samples over a longer period of time would have allowed the assessment of the time course of hormonal changes across individuals (i.e., for the identification of subgroups of subjects based on stress-induced patterns of hormonal reactivity). As mentioned earlier, the use of multiple salivary sampling is an effective way to assess interindividual differences of cortisol variations during basal (e.g., Pruessner et al.; 1997; Pruessner, Gresele & Hellhammer; 1997; Smyth et al., 1997) and stressful periods (e.g., see Deinzer, Kirschbaum, Gresele & Hellhammer, 1997; Lupien et al., 1997).

The data of the present investigation suggested that circulating cortisol was not influenced by any of the impending examinations, and modest elevations of ACTH and prolactin were only observed within 1 hour of the Introductory Psychology examination. Interestingly, more detailed analyses revealed that significant prolactin changes were evident in a subset of subjects. Admittedly, it cannot be said with certainty whether these effects were physiologically meaningful. Nevertheless, distinct patterns of prolactin release were evident between the High and Low BDI groups tested prior to their Introductory Psychology examination. While subjects with High BDI scores showed a marked (67%) increase of circulating prolactin prior to the examination, subjects with Low BDI scores exhibited more modest elevations of this hormone (22%). These data are interesting in that they suggest that neuroendocrine responses to potentially stressful, but anticipated environmental stimuli, may be affected by levels of depressive symptoms. These prolactin data reflect potential HPA disturbances among individuals with subclinical, but notable levels of depressive symptomatology, although such an hypothesis is highly provisional. However, it has been suggested that prolactin variations may be sensitive to graded stressor severity (Armario et al., 1996), and it is conceivable

that the stressors used in the present investigation were perceived as being more aversive when applied on a backdrop of relatively high levels of depressive symptoms.

Like the variations of circulating ACTH and prolactin, alterations of immune activity were associated with the anticipation of examinations. While neutrophil activity was diminished 24 hours prior to the *final* examination session, this measure was unaffected by the anticipation of midterm exams. The differential effects may have been related to the considerable variability associated with this immune measure, or alternatively, were related to the perceived stressfulness of the different examination periods (i.e., midterms being perceived as less stressful or having lesser academic consequences than final examinations). While there have been relatively few investigations that assessed the impact of impending academic examinations on neutrophil activity, in the studies that have been conducted, increases of this immune parameter were observed (see Kang et al., 1996; Kang et al., 1997; 1997). In contrast to the findings of these aforementioned reports, a distinct *decline* of neutrophil activity was observed 24 hours prior to the final examination session. The discrepancy between the data of the present study and the earlier reports may be attributable to the time of measurement relative to the examination challenge. While the previous studies assessed neutrophil activity within the *middle* of the examination period, subjects of present investigation were assessed the *day prior* to their *first final* examination. Thus, it is conceivable that the anticipation of the initial challenge provokes a different pattern of neutrophil activity than that which might be observed among subjects who had already encountered a series of academic challenges within a relatively short period (i.e., adaptation).

In contrast to the neutrophil variations associated with the anticipation of final examinations, there was no evidence to indicate that macrophage activity was affected by the impending examination period. However, we are unable at this time to state with certainty that macrophage activity is unaffected by the anticipation of academic

examinations, as this immune parameter is highly variable, and there are no other comparable studies with human subjects. However, among a nonstressed clinical population, McAdams & Leonard (1993) found increases in monocyte phagocytosis among depressed and manic patients prior to pharmacotherapy. Whether this effect was related to the stress associated with the illness is uncertain.

In contrast to the lack of human studies, several animal studies have reported alterations of macrophage activity in response to stressor exposure (e.g., see Anisman et al., 1997; Ortega, Collazos, Barriga & De la Fuente, 1992; Ortega, Forner, Barriga, & De la Fuente, 1993; Pavlidis & Chirigos, 1980). However, the data from these studies have not provided unambiguous evidence supporting altered macrophage activity in response to stressful stimuli. In part, this stems from the fact that some studies assessed macrophage functioning from blood (e.g., Kizaki, Oh-Ishi & Ohno, 1996; Kizaki, Oh-Ishi Ookawara, Yamamoto & Ohno, 1996; Ortega, Collazos, Barriga & De la Fuente, 1992; Ortega, Forner, Barriga, & De la Fuente, 1993), whereas others examined macrophage functioning in splenic tissue (Anisman et al., 1997; Pavlidis & Chirigos, 1980). Moreover, while some studies assessed the effects of acute stressors, including brief exposure to a predator, cold swim stress, and swimming to exhaustion (e.g., Kizaki, Oh-Ishi & Ohno, 1996; Kizaki et al., 1996; Ortega et al., 1992; 1993), others evaluated the impact of more protracted stressors, including long periods of physical restraint or repeated cold swim exposure (Pavlidis & Chirigos, 1980). In addition to the type and chronicity of the stressors employed, the time at which phagocytic activity was assessed relative to the stressor varied across studies. Finally, there appeared to be considerable variability of the macrophage activity induced by stressors across different strains of rats (e.g., see Anisman et al., 1997).

Despite all the procedural discrepancies between studies, the aforementioned animal experiments demonstrated stress-induced changes of macrophage activity. These outcomes, of course, are at odds with the present findings where the human subjects

failed to show any stress-provoked alterations of macrophage activity. Thus, it is uncertain whether the lack of a stress effect on this immune parameter in human subjects reflects a fundamental species difference between humans and animals, or whether this result is somehow inherent to the study design (e.g., severity of the stressor). The limited data concerning stressor effects on macrophage activity in human subjects precludes the identification of the critical variables involved in this respect. Nonetheless, it is highly probable that many animal experiments use methods that are highly stress-provoking to animals (such as restraint, foot shock, cold swim, predator exposure etc.). Studies in humans have involved severe trauma (e.g., neurogenic stressors such as intractable pain, severe burns; or psychogenic stressors such as chronic caregiving, anticipation of a severe illness such as AIDS) but in none of these reports was macrophage functioning assessed. It is certainly possible that the stress of a final examination to a university student is not sufficiently severe to induce changes of this immune measure.

It is clear from the present series of experiments that stressors may have diverse effects on immune functioning, depending on numerous stressor characteristics (e.g., severity and chronicity), the timing of stressor application relative to blood samples being taken, the individual characteristics of subjects, as well as the specific immune parameters being assessed. Furthermore, it is well established that some immune measures, notably mitogen-stimulated lymphocyte proliferation, are exceedingly variable (Herbert et al., 1994) and, it has been argued that the *in vitro* proliferation of lymphocytes among treated and control subjects should always be conducted in tandem. Thus, it is not entirely unexpected that inconsistent results have been reported concerning the impact of stressors on immune functioning between studies.

Despite these caveats, and in contrast to the neutrophil and macrophage data, a consistent pattern of the proliferation of Con A-stimulated lymphocytes were observed across the three independent experiments. Specifically, cell proliferation was enhanced both one hour, as well as 24 hours, prior to the examination(s). These findings are

commensurate with earlier reports (Kang et al., 1996; Kang et al., 1997; Whitehouse et al., 1996) concerning the impact of an academic exam on the proliferative activity of lymphocytes. However, it is significant that most animal studies that assessed functional immune activity following stressor exposure indicated that environmental insults provoked reductions of mitogen-stimulated lymphocyte proliferation (see reviews in Anisman et al., 1993; Dunn, 1995 & Dantzer & Kelley, 1989).

While there have been far fewer studies assessing the effects of stressors on immune functioning in humans, the bulk of the data (much of it coming from the work of Kiecolt-Glaser, Glaser and their associates) indicated that these stressors elicited an immunosuppressive action (Dorian et al., 1982; Glaser et al., 1986, 1993; Kiecolt-Glaser et al., 1984, 1986, Workman & La Via, 1987). The present findings, obviously, provide an outcome diametrically opposed to these studies. These inconsistencies may be related to any number of procedural differences across experiments, including differences of stressor severity, different populations being studied (medical students vs. first year university students and adolescents), time of sampling relative to the stressor exposure (Glaser et al., 1993; Kang, et al., 1996; Kang et al., 1997; Whitehouse, et al., 1996), as well as variability of perceived importance (and hence, stressfulness) of the academic examination. Unfortunately, the studies that have been conducted in human populations have not yielded sufficient information to identify those variables most cogent in provoking immune alterations (i.e., the enhancement or suppression of immune activity). Interestingly, however, animal studies have suggested that while mild stressors may have an energizing effect (i.e., immunoenhancement), relatively severe stressors provoke suppression of immune functioning (see Anisman et al., 1993; Dunn, 1995; Dantzer & Kelley, 1989; Rinner, Schauenstein, Mangge, Porta, & Kvetnansky, 1992).

It is conceivable that the different stressor-immune effects observed between laboratories may be related to the qualitative nature of the stressors employed. In this respect, the stress of final medical examinations (Glaser et al., 1986; Workman & La Via,

1987), oral presentations (Dorian et al., 1982), natural disasters (Ironson et al., 1997; McKinnon et al., 1989; Weisse et al., 1996), marital difficulties and/or separation (Kiecolt-Glaser et al., 1988; 1994) and the chronic care of a relative suffering from Alzheimer's disease (Kiecolt-Glaser et al., 1996) may be more severe than that of a first year academic examination, hence leading to different immunological outcomes. Moreover, it is notable that there have been only a handful of studies which have demonstrated the immunosuppressive effects of examination stress on mitogen-stimulated T-cell proliferation (Glaser et al., 1986, Halvorsen & Vassend, 1987; Workman & La Via, 1987), and these investigations involved upper year medical students undergoing final medical examinations. In fact, contrary to the immunosuppressive effects observed among medical students, Kang et al. (1996, 1997) reported increased PHA-stimulated cell proliferative activity among adolescents (mean age 16.5 years) during the high school testing period, and these elevations persisted for up to three weeks following examinations. These investigators suggested that the increase of cell proliferative activity demonstrated in their sample could be related to the age of the subjects, as young adults with major depressive disorder were also found to exhibit enhanced lymphocyte proliferation (Schleifer, Keller, Bond, Dohen & Stein, 1996). In this respect, it is notable that subjects in the present investigation were also quite young (mean age approximately 19.5 years). Moreover, there were no apparent correlations between the age of subjects and their proliferative responses to stressors, but this was not surprising given the limited age range of our study population.

In contrast to the effects observed with Con A, a less consistent pattern of lymphocyte proliferation was seen following PHA stimulation. Specifically, in blood samples taken one hour prior to the Introductory Psychology examination, a slight reduction (approximately 15 percent) of T-lymphocyte proliferation was observed among cultures stimulated with 2.5 ug of PHA. The reductions of PHA-stimulated cell proliferation observed during this examination are consistent with those previously

reported among medical students (Glaser et al., 1986; Dorian et al., 1982; Workman & La Via, 1987). However, no changes of this parameter were observed 24 hours prior to the *final* examination (with the exception of a slight increase of the proliferative activity of lymphocytes stimulated with 2.5 ug PHA). Moreover, *enhanced* proliferation of lymphocytes stimulated with PHA was exhibited among subjects tested 24 hours prior to their first *midterm* examination. Taken together, these data suggest that the stress associated with the anticipation of an academic examination among healthy first year university students may provoke different patterns of *in vitro* cell proliferative activity, depending upon the mitogen used in the assay procedures. Moreover, the anticipation of environmental challenges may affect the Con A and PHA dose response curves differently. It is likewise possible that T-cell subtypes are differentially affected by Con A and PHA, and hence the patterns of *in vitro* cell proliferation stimulated by these mitogens may not necessarily be congruent.

In addition to these procedural factors, it is possible that inconsistencies with respect to PHA-stimulated cell proliferation associated with the different examination challenges (i.e., the Introductory Psychology examination, the first midterm and the first final examination) were partially due to the differences of subjects' perception of the quality and/or the consequences of these stressors. As mentioned earlier, the final Introductory Psychology examination, which was typically written at the end of the examination session, may have been construed as a signal for the end of a fairly protracted stressful period (i.e., the 2-3 weeks of the examination session). It is conceivable that by this particular time within the examination period, the development of some biological and/or behavioral adaptational processes had occurred, which differentially affected the proliferative activity of lymphocytes stimulated with PHA. In contrast, an *enhancement* of this immune measure was observed (at all PHA doses) among subjects who were tested prior to the first exam within the *midterm* examination session. It was unlikely that the students tested prior to their *midterm* exam had

encountered any previous university level examinations (Experiment 3) and, thus, would not have had the same opportunity to develop biological and/or behavioral adaptational processes. In contrast, subjects tested prior to their Introductory Psychology examination had likely written several university examinations. As such, it is conceivable that level of experience with this type of challenge could influence biological and/or behavioral adaptational processes culminating in different dose response patterns with Con A and PHA. However, these hypotheses are speculative, and require further study.

Perceived stressor severity and the characteristics of the target population are important factors when considering the impact of stressors. It was likely that in the present investigation a proportion of subjects did not perceive the exam situation as stressful. Subjects may have adapted to the psychological stress associated with the impending exams, or there may have been adaptation in terms of the neurochemical and immune changes that might have been elicited by acute, unpredictable stressors. As indicated earlier, the examination period could also be perceived as having positive and/or relaxing values, as it signals the end of the academic year, and the impending opportunity to vacation. In effect, the perceived stress of the examination may have been attenuated, hence favoring elevated levels of cell proliferation (similar to immunoenhancement that may be observed following mild stressor exposure; e.g., Rinner et al., 1992). In support of this supposition was the finding that mean Perceived Stress Scale scores did not change between the baseline, examination or even the post-examination sampling periods. While these data may be considered somewhat surprising, identical data were obtained among graduate students whose stress perception was measured at various times relative to their oral thesis defense (Lacey et al., 1998, unpublished report).

Although it is reasonable to suggest that the perceived stress of day-to-day events may be independent of the perceived stress associated with an academic examination, such does not appear to be the case for subjects in the present report. Subjects rated their

examination-specific anxiety as "average" (i.e., mean ratings = 4.4, 4.5 and 4.4 on a 7 point likert scale for the three independent experiments). Moreover, only a small (13-18) percent of subjects rated the impending examination as highly stress-provoking (a rating of 6 out of 7). Interestingly, in the studies that reported *reduced* cell proliferative activity in response to academic testing, significant increases of examination-specific perceived stress and/or anxiety were observed relative to baseline levels (Dorian et al., 1982; Maes et al., 1998). It seems counterintuitive, however, that most subjects in the present study did not report greater perceived stress in anticipation of examinations compared to baseline levels. The source for this paradoxical outcome is not immediately evident, but the Perceived Stress Scale which was used to monitor stress perception may not have been provided an unambiguous index of anticipatory stress.

The anxiety or stress perception associated with academic challenges may have very different endocrine and/or immunological consequences across different student populations. Among graduate students, an oral thesis defense was sufficiently stressful to provoke elevations of circulating cortisol, but cell proliferative activity appeared to be unchanged relative to baseline. Yet, when these graduate students were assessed 6 weeks prior to their oral examination, Con A-stimulated cell proliferation was reduced relative to that observed among age- and gender-matched control subjects (Lacey et al., 1998). While the lack of changes of cell proliferative activity *immediately prior* to the oral defense could have been attributed to the chronic nature of graduate students' program of study (and, hence, the development of adaptational processes), it does not explain the immunosuppression observed *6 weeks prior* to the thesis defense. Such an effect, in fact, could be attributed to characteristics specific to this student population in conjunction with the nature of the work in which they were involved. Graduate students, unlike first year university students, or medical students for that matter, have control over the actual date of their oral defense. Unlike medical students, who have predetermined examination dates, graduate students set the time of their oral defense depending on when they feel

they can successfully defend the thesis. As such, the preparation and/or anxiety associated with the actual thesis submission, as well as the preparation for the oral presentation, may occur weeks before the actual defense. Accordingly, it is not altogether surprising that immune activity may be somewhat compromised at this time. It is conceivable that considerable alleviation of anxiety occurs following the submission of the written thesis, meetings with the academic advisor, as well as successful rehearsals of the oral defense. In effect, over the course of a few weeks, feelings of confidence and/or mastery are likely enhanced, and thus lymphocyte proliferative activity may not be compromised at the time of the oral defense (Lacey et al., 1998). As such, the immunological consequences of academic testing among medical students (or, among first year university students, for that matter) who do not have control of the time of their examinations may have patterns of endocrine and/or immune responses to these challenges that are distinct from those seen among graduate students.

It will be recalled that among a subset of subjects of the present investigation, marked declines of both Con A and PHA-stimulated cell proliferation were observed 10 to 14 days after the cessation of the final examination period. This decline was evident with respect to the values seen immediately before the examination, as well as at baseline (4 - 6 weeks earlier). The reduction was apparent with all of the doses of PHA, as well as the 2.0 and 5.0 ug doses of Con A. These observations are consistent with data reported by Workman and La Via (1987), who demonstrated marked reductions of PHA-stimulated cell proliferation one to four weeks following the American National Board Medical Examinations (relative to control subjects). However, the present data are inconsistent with those reported by Dorian et al. (1982) who examined highly stressed medical students (as defined by General Health Questionnaire scores) and Kang et al. (1996; 1997) who assessed these measures among adolescents. In both of these studies, which assessed subjects 2-3 weeks after academic examinations, *increases* of PHA-

(Kang et al., 1996; 1997) and Con A- (Dorian et al., 1982) stimulated cell proliferation were observed relative to pre-examination values.

The mechanisms accounting for the different patterns of examination-related immune activity between the aforementioned studies and the present report are not known. Once again, it seems possible that factors involving subject characteristics, time of the post-exam sampling, or the pattern of changes (or lack thereof) of the stress perception associated with the examination may have contributed in this respect. However, the possibility needs to be considered that the decline of *in vitro* cell proliferative activity observed 10-14 days following the cessation of the examination period among subjects of the present investigation may simply represent a normalization to the "real" basal levels of immune activity, and the baseline and pre-exam measures of cell proliferation represent elevations of immune activity. From this perspective, the cell proliferation seen at baseline and prior to the examination session may both represent elevations of immune functioning, possibly reflecting the stress associated with the school year (see Arthur, 1998). Of course, a more detailed and lengthy prospective analysis would be necessary in order to validate this hypothesis.

Endocrine & Behavioral Correlates of Alterations of Immune Activity Associated with the Academic Examination

The present investigation assessed whether the changes of hormonal and sympathetic activity associated with the examination challenges would predict the changes of immune activity. In general, it seemed that the alterations of cell proliferation observed prior to the examination were independent of the changes of plasma hormones. However, given that the hormonal and immune parameters were assessed using single stick sampling, we cannot state with certainty that the alterations of immune activity were *completely* independent of hormonal variations. As mentioned earlier, cortisol is released in pulses and levels are sustained for a relatively short period of time. As such, single stick sampling may not be an accurate index of circulating glucocorticoids. Additionally,

the changes of circulating lymphocytes and their activity do not occur instantaneously, and like the cortisol changes, are dynamic in nature. Clearly, it is exceedingly difficult to gauge the relationship between two (or more) dynamic biological processes by using static measures taken within a narrow window of time.

Despite the dynamic nature of the hormonal and immunological activity, the changes of prolactin attributable to the examination challenges predicted the changes of cell proliferative activity. Subjects who showed greater elevations of circulating prolactin prior to the examination tended to exhibit greater elevations of Con A-stimulated cell proliferation. While mechanism(s) subserving the relationship between the prolactin changes and the immune alterations are not clear, it is known that prolactin receptors exist on B- and T-cell populations. In addition to prolactin being released from the pituitary, both B- and T-cells are known to secrete a prolactin-like substance *in vitro* (see Reber, 1993 for review). At physiological levels, prolactin may serve both a trophic function (i.e., for proliferative responses to immunological challenges, and perhaps stressor exposure) and may promote T-cell activation (Draca, 1995; Jurcovicova, Kruneger, & Rokyta, 1997; Reber, 1993). Since either very low or very high levels of this hormone inhibit lymphocyte proliferation *in vitro*, it is conceivable that the magnitude of stressor-provoked prolactin changes could determine the magnitude and direction of *in vitro* functional immune activity. Inasmuch as subjects in the present investigation showed relatively modest increases (about 25%) of circulating prolactin prior to the examination, it is not unexpected that the hormonal changes predicted the changes of cell proliferation. Indeed, the increases of this circulating hormone may have been sufficient to promote an overall elevation of cell proliferative activity, but not so much that an immunosuppression was observed.

One of the possible mechanisms underlying the relationship between the prolactin changes and the alterations of proliferative activity involves potential variations of levels of circulating cytokines elicited by stressful events. It was recently demonstrated that

increases of IL-1 receptor antagonist, interferon γ (IFN- γ), tumour necrosis factor- α (TNF- α) as well as IL-6 were evident among "highly stressed" medical students one day prior to a difficult academic examination (Maes et al., 1998). It seems possible that the changes of circulating cytokines, as well as their respective receptors, may alter the ability of circulating prolactin levels to affect functional immune activity. Specifically, it has been proposed that prolactin acts cooperatively with IL-2 to promote cell proliferation *in vitro*. Prolactin upregulates surface receptors for IL-2 on lymphocytes, which in turn, promotes the nuclear translocation of prolactin into the nucleus of these cells. The internalized prolactin acts as a necessary growth factor for cell proliferative activity, particularly with respect to the S phase of cell growth (see Reber, 1993). Moreover, *in vitro*, physiological levels of prolactin potentiate the stimulatory effects of IL-2 on cell proliferation. However, by itself, prolactin does not appear to stimulate lymphocyte proliferation in culture (Jurcovicova, Krueger, Rokyta, 1997). Thus, it is conceivable that the anticipation of the examination in the present investigation could have affected levels of cytokines and their receptors, including IL-2, culminating in the enhancement of *in vitro* cell proliferative activity. Of course, it remains to be determined whether significant (and biologically relevant) changes of circulating cytokines are related to changes of *in vitro* immune activity prior to an examination challenge among first year university students (particularly among those who do not show exam-related increases of stress perception).

As with the basal immune measures, we assessed whether the stress-related variables and/or the Quality of Life indices, could account for the variability of the hormonal and immune alterations associated with an academic examination. Curiously, subjects who reported greater severity (and frequency) of daily hassles were more likely to display *attenuated* increases of cortisol, prolactin and epinephrine immediately prior to the Introductory Psychology examination, irrespective of their level of depressive symptomatology. Likewise, subjects who experienced more intense major life events

exhibited attenuated changes of cell proliferation associated with the examination. In effect, it appeared that subjects who experienced either more intense major life events and/or perceived their daily hassles as more severe were *less* likely to be *biologically reactive* to an impending examination challenge. These findings are consistent with those of earlier studies which examined the changes of circulating NK cell number and NK cytotoxicity associated with stressor exposure. In particular, elevations of circulating NK cell numbers and reduced NK cytotoxicity were observed among nondepressed subjects undergoing chronic life stress (see Brosschot et al., 1994; Evans et al., 1995; McKinnon et al., 1989; Ironson et al., 1997). Moreover, among chronic, but mildly depressed (dysthymic) subjects, stressor history was found to be associated with circulating NK cell number. Specifically, while mild stressors ordinarily increased the number of circulating NK cells, stressor history was inversely related to NK cell number (Ravindran et al., 1996a). Given the aforementioned findings, coupled with the present data, it is conceivable that repeated stressor exposure (i.e., in the form of daily hassles or major life events) induces the development of adaptational processes, which culminates in *attenuated* immune and/or endocrine activity that might normally precede an impending challenge. As will be seen shortly, this hypothesis is consistent with the associations found between the changes of cell proliferative activity and stress perception, as well as Mastery and Life Satisfaction.

It was apparent that greater stress perception (as a lone variable) was associated with *reductions* of cell proliferative activity prior to the final examination period. Interestingly, this relationship was not significant when levels of Mastery and Life Satisfaction were considered. Subjects' Mastery and Life Satisfaction scores (both of which were negatively associated with stress perception) were highly correlated with the changes of cell proliferative activity observed prior to the final examination period. Given that Life Satisfaction predicted both basal and examination-related immune activity, it is conceivable that this variable, relative to stress perception, could be a more

reliable predictor of immune changes associated with relatively mild stressors. Of course, it is also possible that among student populations where exemplary academic performance may not be as crucial (in contrast to studies which used medical students), the perceived stress associated with the impending examinations may not be as considerable (as was demonstrated in the present investigation). Accordingly, under these conditions, the predictive capacity of stress perception on changes of immune activity may not be particularly powerful. As such, other quality of life or personality variables, including Life Satisfaction and Mastery, may be better predictors of the immune changes associated with moderately challenging stressors. Of course, these particular findings need to be replicated using larger sample sizes.

In addition to stressor history, Mastery or Life Satisfaction, the endocrine and immune responses associated with the academic examinations could be predicted by subjects' coping profiles. In particular, the use of either Emotional Expression plus Social Support Seeking or Emotional Containment plus Passivity was negatively correlated with the changes of plasma prolactin observed prior to the Introductory Psychology examination. In fact, approximately 14 percent of the variance of the changes of plasma prolactin could be accounted for when BDI scores were considered together with Emotional Expression plus Social Support Seeking. In effect, persons who showed greater depressive symptomatology, and favored the use of Emotional Expression plus Social Support Seeking, were *less* likely to show elevations of prolactin prior to this examination. The relationship between the coping strategies used and the changes of plasma prolactin is consistent with the finding that Con A-stimulated cell proliferation was somewhat attenuated among subjects who favored the use of Emotional Containment plus Passivity.

Taken together, it seems that the hormonal and immunological reactivity to a stressful stimulus of a mild to moderate nature, such as an academic examination, may be influenced by subject characteristics, including stressor history, coping profiles, and

quality of life indices, such as Life Satisfaction. In this respect, it seems plausible that a certain degree of hormonal and/or immunological reactivity to stressors may, in fact, be more adaptive for minimizing the potential biological disturbances that otherwise might be provoked by sustained stressor exposure. Thus, individuals who show significant, but subclinical levels of depressive symptomatology may not show the appropriate degree of hormonal or immune reactivity that would be optimally expected in the face of an expected challenge.

Alterations of Basal Immune Activity Among Depressive Subtypes

It will be recalled that depressive illness has been associated with alterations of HPA activity, as well as changes of enumerative and functional immune parameters (see Holsboer, 1995; Maes, 1995; O'Leary, 1990; Stein, 1991; Weisse, 1992 for reviews). The possibility was considered in the present investigation that the immune alterations were related to illness characteristics, including the chronicity of the affective disturbance, as well as the presence of typical vs. atypical symptomatology. As discussed earlier, the variations of immune activity have primarily been observed among persons with major depression, particularly those with melancholia who are most likely to demonstrate abnormalities of HPA activity (e.g., abnormal DSTs) (Maes, 1995; Weisse, 1992). However, it is possible that other subtypes of depressive illness (such as dysthymia) not normally associated with these HPA abnormalities (see Howland & Thase, 1991; Howland & Thase, 1995; Ravindran et al., 1994; Ravindran et al., 1997) might also display immune disturbances. As discussed earlier, both major depressive and dysthymic subjects showed elevated numbers of circulating NK cells, which normalized with successful pharmacotherapy. However, such an outcome required a longer treatment period among dysthymic patients (i.e., 12 weeks of pharmacotherapy among MDD subjects vs. 6 months or more among persons with dysthymia; Ravindran et al., 1995a). The fact that dysthymic patients exhibited immune disturbances in the absence of cortisol

variations suggests, at least provisionally, that this endocrine was not fundamental in accounting for the immune disturbances.

In addition to illness chronicity, the characteristic symptoms of the depression may determine both the HPA and immune profiles. It will be recalled that symptoms of typical major depressive disorder involve neurovegetative disturbances, including reduced sleep, eating, as well as weight loss. In contrast, atypical features comprise reversed neurovegetative symptoms, such as increased sleeping, eating, weight gain, and leaden paralysis. Additionally, persons with atypical depression tend to show increased mood reactivity, as well as rejection sensitivity (American Psychiatric Association, 1994). Further, atypical depression may be associated with neuroendocrine characteristics that are distinguishable from those of typical major depression. Specifically, atypical depressive illness was associated with elevated levels of plasma ACTH, but reduced circulating cortisol concentrations (Anisman et al., 1998). Given the potential interplay between neuroendocrine and immune activity, as well as potential effects of neurovegetative functioning on neuroendocrine activity, it is possible that illness characteristics may influence the functional immune activity associated with depressive illness. In fact, it was demonstrated that circulating NK cells were elevated among male patients with typical major depression, but not among patients exhibiting atypical features (Ravindran, Griffiths, Merali & Anisman, 1998). Moreover, while persons with atypical major depressive illness showed increased serum IL-1 β levels, this was not the case among patients that displayed typical features (Griffiths, Ravindran, Merali & Anisman, 1996; Anisman et al., 1998). Interestingly, however, it was observed that irrespective of the neurovegetative characteristics, the production of IL-1 β *in vitro* (i.e., from mitogen-stimulated lymphocytes) was elevated among dysthymic patients, but not among patients with MDD (Anisman et al., 1998). Thus, in the present investigation, the possibility was considered that the chronicity of illness (i.e. MDD vs. dysthymia), as well as the presence of atypical vs. typical symptomatology, might affect functional immune activity, and that

the immune variations following SSRI treatment would normalize with the alleviation of depressive symptoms.

In the present study, it was observed that irrespective of their neurovegetative profiles, prior to pharmacotherapy, dysthymic subjects exhibited lower levels of lymphocyte proliferative activity relative to both MDD patients and nondepressed controls. In general, cell proliferation among individuals with atypical MDD did not differ from that observed among the control subjects. However, individuals with typical MDD tended to exhibit lower levels (approximately 45%) of Con A-stimulated (5.0 ug) cell proliferation relative to control subjects. While it is tempting to suggest that immune activity may vary according to the neurovegetative features of the depressive illness, conclusions concerning the differential outcomes observed between patients with typical vs. atypical major depression must be tempered by the small sample represented in the present report.

The findings of the present investigation indicate that either Con A- or PHA-stimulated cell proliferative activity is sensitive to the chronicity of illness, irrespective of the neurovegetative features. However, while the reduction of Con A-stimulated cell proliferative activity among the typical major depressives (relative to controls) is consistent with those previously reported (e.g., Calabrese, et al., 1987; Cosyns, et al., 1989; Darko, et al., 1986; Kronfol & House, 1984; Levy, Fernstrom, Herberman, et al., 1991; McAdams & Leonard, 1993; Schleifer et al., 1984; Syvalahti, Eskola, Ruuskanen, & Laine, 1985), if these measures are examined *without* considering the neurovegetative profiles, then no differences are evident between MDD and control subjects. This finding was also observed in other investigations (e.g., see Bauer et al., 1995a; Hickie et al., 1993). Unfortunately, as the data provided in many earlier reports are not sufficiently detailed to allow determination of whether subjects comprised a mixed population of depressive patients (although this likely was the case), appropriate comparisons cannot be made between the present findings and these earlier investigations.

It is noteworthy that although the severity of illness is less profound in dysthymic patients than in the major depressive subjects, the diminished lymphocyte proliferation was more pronounced in the chronic illness. Thus, these data support the contention that in addition to severity, the duration of illness may be fundamental in determining the nature of the immune alterations associated with depressive symptomatology. In their analysis, Anisman et al. (1998) likewise reported that dysthymia was associated with altered mitogen-stimulated IL-1 β production, and the magnitude of this effect was directly related to the duration of illness. In contrast, while cell proliferative activity was markedly decreased among dysthymic subjects, the degree of disturbance was neither predicted by illness duration nor the age of onset of the illness.

The decline of the proliferative immune responses among the dysthymic subjects were likewise not related to the presence of typical vs. atypical symptoms. Recent findings in our laboratory indicated that these defining characteristics of the depressive illness may contribute to the inconsistency of the immune changes that have been associated with depression. As mentioned earlier, persons with atypical major depression exhibited elevations of plasma ACTH and increased levels of circulating IL-1 β , whereas among dysthymic subjects (and not those with major depression), elevations of mitogen-stimulated IL-1 β production were evident irrespective of the neurovegetative features (Anisman et al, 1998). Unfortunately, as the association between the severity of *individual* atypical symptoms (as measured by items 23 - 28 of the 29-item HAM-D) were not analyzed in relation to the basal immune measures (in our attempts to reduce the number of statistical tests), it is uncertain whether any *one* or more of these neurovegetative characteristics in combination, accounted for the marked reduction of cell proliferation among dysthymic subjects in the present report.

In addition to elevations of IL-1 β production, Anisman et al. (1998) reported that depressive illness was associated with reduced IL-2 in supernatants of mitogen-stimulated lymphocytes. However, as indicated by these investigators, their IL-2 assay

did not involve the use of anti-tac (an IL-2 receptor blocking antibody), and hence, it is uncertain whether depressive illness was associated with reduced IL-2 production or altered binding with IL-2 receptors (Baroja & Cueppens, 1987). It is nonetheless conceivable that the changes of IL-2 (a T-cell proliferative factor) observed among dysthymic individuals, could be related to the decline of cell proliferative activity observed in the present investigation.

Given the reduction of cell proliferation associated with dysthymia, it is tempting to suggest that the immune dysfunction was secondary to the mood disorder. Thus, it might be expected that normalization of immune functioning might accompany the alleviation of depressive symptoms. However, overall, the diminished cell proliferation among dysthymic subjects was not modified by SSRI treatment, at least within the 12 week treatment period. This finding parallels the data reported by Ravindran et al. (1995a) who showed that relative to persons with MDD, the normalization of elevated circulating NK cells required a longer period of pharmacotherapy (i.e., 6 months or greater) among dysthymic patients. Likewise, in the present study, analyses of the dysthymic subjects who *responded* to the pharmacotherapy, revealed a 35% *increase* of Con A-stimulated cell proliferation (however, this effect was just shy of statistical significance). In contrast, persons with MDD who responded to treatment displayed a *reduction* of both Con A and PHA-stimulated lymphocyte proliferation between baseline and week 12. Inasmuch as there were few MDD treatment *nonresponders*, it was not possible to determine whether the decline of cell proliferative activity exhibited among MDD treatment responders was due to symptom alleviation or secondary to the effects of the SSRI pharmacotherapy. However, it has been reported that treatment with desmethylinipramine reduced *in vitro* mitogen-induced cell proliferation among depressed individuals (Fu, Jarvik, Yen & Matsuyama, 1977). Moreover, reduced proliferation of lymphocytes stimulated with either Con A and PHA were observed following 3-6 weeks of either tricyclic antidepressant or lithium treatment among MDD

patients (Albreicht, Helderman, Schlessner, & Ruh, 1985). Together, these findings suggest that tricyclic agents, and potentially, SSRIs, can effectively attenuate the altered cell proliferation associated with depressive illness.

The mechanisms which subserved the cell proliferative changes among either the major depressive or dysthymic subjects following SSRI treatment could not be identified. However, it is possible that some of these immune variations could be secondary to changes of circulating cytokines observed following pharmacotherapy (Maes, Bosmans, DeJongh, Kenis, Vandoolaeghe & Neels, 1997; Sluzewska et al., 1996; Weizman et al., 1994). This supposition is highly provisional as few studies have assessed the influence of antidepressant treatment on circulating cytokines, and those studies only examined such effects among major depressive subjects (whose atypical symptomatology was not considered; Maes, Bosmans, DeJongh, Kenis, Vandoolaeghe & Neels, 1997; Sluzewska et al., 1996; Weizman et al., 1994). Nonetheless, inasmuch as dysthymic illness is associated with both IL-1 and IL-2 alterations, it might be profitable to determine whether both changes of circulating cytokines and cell proliferative activity occur among these individuals following sustained SSRI treatment of a longer duration (e.g., 6 months or more).

Summary

The results of the present report indicated that among a nondepressed student population, stressful events may impact on various aspects of immune functioning. However, the variations of immune and neuroendocrine activity are dependent upon the type (laboratory vs. naturalistic), timing, and severity (mild vs. more severe) of the stressor examined. In general, laboratory challenges neither provoked alterations of endocrine nor immune activity. In contrast, anticipation of mild-moderately severe naturalistic stressors, namely, academic examinations, were sufficient to provoke an enhancement of the proliferative activity of lymphocytes. Modest increases of circulating hormones (ACTH, prolactin, NE and Epi) were detected within 1 hour, but not 24 hours

prior to an academic examination. These data indicate that the anticipation of a mild-moderate naturalistic stressor may provoke alterations of functional immune activity which appear sooner (at least 24 hours) than hormonal alterations. These data might be taken to suggest that the immunoenhancement may be independent of changes of hormonal or sympathetic activity. Of course, the assessment of these stressor-provoked immune and endocrine changes is complicated by the single stick sampling procedure employed, as well as the considerable interindividual variability of biological and behavioral reactivity to environmental challenges.

Nonetheless, the present report provides evidence to suggest that (a) individuals who show subclinical indications of depressive symptomatology and/or more exaggerated stressor history are *less* likely to exhibit changes of hormonal and immune activity prior to an academic challenge, whereas (b) individuals who report minimal depressive symptomatology and/or minimal stressor history coupled with enhanced levels of Quality of Life (i.e., Life Satisfaction) are those who exhibit the greatest immunological reactivity in response to the anticipation of impending academic challenges. These findings imply that a certain degree of biological reactivity may be part of the adaptational responses that occur in response to expected environmental challenges of mild - moderate severity, and that even subclinical levels of depressive symptomatology may impair these adaptive responses. While the mechanisms which subserve these relationships cannot be elucidated from the present data, it is possible that significant, but *subclinical* levels of depressive symptomatology are associated with particular behavioral profiles (e.g., greater stressor history, favored use of emotion-focused coping and reduced quality of life) that promote impairment of HPA feedback mechanisms. Ultimately, such alterations might translate into reduced biological reactivity to subsequent stressors.

Among individuals with *clinical* levels of depression (i.e., dysthymic disorder or major depression of moderate severity), immune activity appears more dependent upon

the chronicity rather than severity or the neurovegetative aspects of the illness (at least with respect to the mild-moderate range of depressive illness). Like severe, melancholic depression, dysthymic disorder is also associated with reduced levels of functional immune activity. Given that individuals with this chronic depressive illness show changes of IL-1 and IL-2 production (Anisman et al., 1998), it is conceivable that these changes might contribute to the reduced cell proliferative measures.

Finally, the findings of the present report suggest that successful SSRI treatment among dysthymic subjects may be associated, to some degree, with an increase of functional immune activity. Like the normalization of circulating NK cells observed following pharmacotherapy (see Ravindran et al., 1995a), it is conceivable that sustained SSRI treatment over a longer period (i.e., 6 months) might result in further, if not complete, normalization of the *in vitro* proliferative activity of lymphocytes. Whether concomitant cytokine alterations occur with the normalization of functional immune activity among successfully treated dysthymic patients remains to be assessed. Likewise, the effects of successful pharmacotherapy on functional immune activity and other related cytokine measures in atypical major depressive illness need to be elucidated.

References

- Ader, R., & Cohen, N. (1991). The influence of conditioning on immune response. In R. Ader, D. S. Felten, & N. Cohen (Eds.), Psychoneuroimmunology (pp. 611-646). San Diego: Academic.
- Adler, N. (1994). Health psychology: Why do some people get sick and some stay well? Annu. Rev. Psychol., 45, 229-259.
- Akiskal, H. S. (1990). Towards a definition of dysthymia: Boundaries with personality and mood disorders. In S. W. Burton & H. S. Akiskal (Eds.), Dysthymic Disorders pp. 1.
- Akiskal, H. S. (1989). Validating affective personality types. In L. Robins & J. Barret (Eds.), The validity of psychiatric diagnosis (pp. 217-227). New York: Raven Press.
- Albrecht, J., Helderman, J.H., Schlessner, M.A., & Rush, A.J. (1985). A controlled study of cellular immune function in affective disorders before and during somatic therapy. Psychiat. Res., 15, 185-193.
- Aldwin, C. M. (1994). Stress, Coping and Development. An Integrative Perspective. New York: Guilford Press.
- American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Washington: American Psychiatric Association.
- Anisman, H., Merali, Z., Griffiths, J., & Ravindran, A. V. (1998). Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. Mol. Psychiat., submitted.
- Anisman, H., Lu, Z. W., Song, C., Kent, P., McIntyre, D. C., & Merali, Z. (1997). Influence of psychogenic and neurogenic stressors on endocrine and immune activity: Differential effects in fast and slow seizing rat strains. Brain, Behav. Immun., 11, 63-74.
- Anisman, H., & Zacharko, R. M. (1990). Multiple neurochemical and behavioral consequences of stressors: Implications for depression. Pharm. Ther., 46, 119-136.

- Anisman, H., Zalcman, S., Shanks, N., & Zacharko, R. M. (1991). Multisystem regulation of performance deficits induced by stressors: An animal model of depression. In A. Boulton, G. Baker, & M. Martin-Iverson (Eds.), Neuromethods (pp. 1-59). New Jersey: Humana Press.
- Anisman, H., Zalcman, S., & Zacharko, R. M. (1993). The impact of stressors on immune and central neurotransmitter activity: Bidirectional communication. Rev. Neurosci., 4, 147-180.
- Antoni, F. A. (1986). Hypothalamic control of adrenocorticotropin secretion: advances since the discovery of 41-residue corticotropin-releasing factor. Endocr. Rev., 7, 351-378.
- Armario, A., Merti, O., Molina, T., Depablo, J., & Veldes, M. (1996). Acute stress markers in humans: response of plasma glucose, cortisol and prolactin to two examinations differing in anxiety they provoke. Psychoneuroendocrinology, 21, 17-24.
- Arthur, N. (1998). The effects of stress, depression, and anxiety on postsecondary students' coping strategies. J. College Student Develop., 39, 11-22.
- Bachen, E. A., Manuck, S. B., Marsland, A. L., Cohen, S., Malkoff, S. B., Muldoon, M. F., & Rabin, B. S. (1992). Lymphocyte subset and cellular immune responses to a brief experimental stressor. Psychosom. Med., 54, 673-679.
- Baroja, M. .L., & Cueppens, J. L. (1987). More exact quantification of interleukin-2 production by addition of anti-Tac monoclonal antibody to cultures of stimulated lymphocytes. J. Immunol. Meth., 98, 267-270.
- Baron, R. W., Cutrona, C. E., Hicklin, D., Russell, D. W., & Lubaroff, D. M. (1990). Social support and immune function among spouses of cancer patients. J. Pers. Soc. Psychol., 59, 344-352.

- Bauer, M. E., Gauer, G. J., Luz, C., Silveira, R. O., Nardi, N. B., & von Muhlen, C. A. (1995a). Evaluation of immune parameters in depressed patients. Life Sci. **57**, 665-674.
- Bauer, M. E., Hohagen, F., Gimmel, E., Bruns, F., Lis, S., Krieger, S., Ambach, W., Guthmann, A., Grunze, H., Fritsch-Montero, R., Weissbach, A., Ganter, U., Frommberger, U., Riemann, D., & Berger, M. (1995b). Induction of cytokine synthesis and fever suppresses REM sleep and improves mood in patients with major depression. Biol. Psychiatry, **38**, 611-621.
- Beck, A. T., & Beck, R. W. (1972). Screening depressed patients in family practice: A rapid technique. Postgrad. Med., **Dec.**, 81-85.
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. Arch. Gen. Psychiatry, **4**, 561-569.
- Beckham, E. E., & Adams, R. L. (1984). Coping behavior in depression: Report of a new scale. Behav. Res. Ther., **22**, 71-75.
- Benschop, R. J., Brosschot, J. F., Godaert, G. L. R., Smet, M. B. M. D., Geenen, R., Olff, M., Heijnen, C. J., & Ballieux, R. E. (1994). Chronic stress affects immunological but not cardiovascular responsiveness to acute psychological stress in humans. Am. J. Physiol., **266**, R75-R80.
- Benschop, R. J., Jacobs, R., Sommer, B., Schurmeyer, T. H., Raab, H. R., Schmidt, R. E., & Schedlowski, M. (1996). Modulation of the immunological response to acute stress in humans by beta-blockade or benzodiazepines. FASEB J., **517-524**, 517-524.
- Benschop, R. J., Nieuwenhuis, E. E. S., Tromp, E. A. M., Godaert, G. L. R., Ballieux, R. E., & van Dooren, L. J. P. (1994). Effects of β -adrenergic blockade on immunologic and cardiovascular changes induced by mental stress. Circulation, **89**, 762-769.

- Benschop, R. J., Rodriguezfeverhahn, M., & Schedlowski, M. (1996). Catecholamine-induced leukocytosis - Early observations, current research, and future directions. Brain Behav. Immun., 10, 77-91.
- Berkenbosch, F., Van Oers, J. W. A. M., del Rey, A., Tilders, F. J. H., & Besedovsky, H. O. (1987). Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. Science, 238, 524-526.
- Besedovsky, H. O., del Rey, A., Klusman, I., Furukawa, H., Ardit, G. M., & Kabiersch, A. (1991). Cytokines as modulators of the hypothalamic-pituitary-adrenal axis. J. Steroid Biochem. Molec. Biol., 40, 613-618.
- Blalock, J. E. (1994). The syntax of immune-neuroendocrine communication. Immunology Today, 15, 504-511.
- Brosschot, J. F., Benschop, R. J., Godaert, G. L. R., Olf, M., Smet, M. D., & Heijnen, C. J. (1994). Influence of life stress on immunological reactivity to mild psychological stress. Psychosom. Med., 56, 216-244.
- Brosschot, J. F., Benschop, R. J., Godaert, G. L. R., Smet, M. B. M. D., Olf, M., Heijnen, C. J., & Ballieux, R. E. (1992). Effects of experimental psychological stress on distribution and function of peripheral blood cells. Psychosom. Med., 54, 394-406.
- Brown, G. W. (1993). Life events and affective disorder: Replications and limitations. Psychosom. Med., 55, 248-259.
- Brown, G. W., Bifulco, A., & Harris, T. O. (1987). Life events, vulnerability and onset of depression - some refinements. Br. J. Psychiatry, 150, 30-42.
- Cacioppo, J. T., Malarkey, W. B., Kiecolt-Glaser, J. K., Uchino, B. N., Sgoutas-Emch, S. A., Sheridan, J. F., Berntson, G. G., & Glaser, R. (1995). Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation. Psychosom. Med., 57, 154-163.

- Caggiula, A. R., McAllister, C. G., Matthews, K. A., Berga, S. L., Owens, J. F., & Miller, A. L. (1995). Psychological stress and immunological responsiveness in normally cycling, follicular-stage women. J. Neuroimmunol., 59, 103-111.
- Calabrese, J. R., Kling, M. A., & Gold, P. W. (1987). Alterations in immunocompetence during stress, bereavement, and depression: Focus on neuroendocrine regulation. Am. J. Psychiatry, 144, 1123-1134.
- Carroll, B. J. (1982). The dexamethasone test for melancholia. Br. J. Psychiatry, 140, 292-304.
- Charles, G., Machkowski, R., Brohee, D., Wilmotte, J., & Kennes, B. (1992). Lymphocyte subsets in major depressive patients. Neuropsychobiol., 25, 94-98.
- Checkley, S. (1996). The neuroendocrinology of depression and chronic stress. Brit. Med. Bull., 52, 597-617.
- Christensen, A. J., Edwards, D. L., Wiebe, J. S., Benotsch, E. G., McKelvey, L., Andrews, M., & Lubaroff, D. M. (1996). Effect of verbal self-disclosure on natural killer cell activity: Moderating influence of cynical hostility. Psychosom. Med., 58, 150-155.
- Chrousos, G. P., & Gold, P. W. (1992). The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA, 267, 1244-1252.
- Clover, R. D., Abell, T., Becker, L. A., Crawford, S., & C.N. Ramsey, J. (1989). Family functioning and stress as predictors of influenza B infection. J. Fam. Pract., 28, 535-539.
- Cobb, J. M. T., & Steptoe, A. (1996). Psychosocial stress and susceptibility to upper respiratory illness in an adult population sample. Psychosom. Med., 58, 404-412.
- Cohen, J. J. (1987). Immunity and behavior. J. Aller. Clin. Immunol., 79, 2-5.
- Cohen, S. (1988). Psychosocial models of the role of social support in the etiology of physical disease. Health Psychol., 7, 269-297.

- Cohen, S., & Herbert, T. B. (1996). Health psychology: Psychological factors and physical disease from the perspective of human psychoneuroimmunology. Annu. Rev. Psychol., 47, 113-42.
- Cohen, S., Karmarck, T., & Marmelstein, R. (1983). A global measure of perceived stress. J. Health Hum. Behav., 24, 385-396.
- Cohen, S., Line, S., Manuck, S. B., Rabin, B. S., Heise, E. R., & Kaplan, J. R. (1997). Chronic social stress, social status, and susceptibility to upper respiratory infections in nonhuman primates. Psychosom. Med., 59, 213-221.
- Cohen, S., & Williamson, G. M. (1991). Stress and infectious disease in humans. Psych. Bull., 109, 5-24.
- Cosyns, P., Maes, M., Vanderwoude, M., et al. (1989). Impaired mitogen-induced lymphocyte responses and the hypothalamic-pituitary-adrenal axis in depressive disorders. J. Affect. Disord., 16, 41-48.
- Croiset, G., Heijnen, C. J., Veldhuis, H. D., de Wied, D., & Ballieux, R. E. (1987). Modulation of the immune response by emotional stress. Life Sci., 40, 775-782.
- Dallman, M. F. (1993). Stress update adaptation of the hypothalamic-pituitary-adrenal axis to chronic stress. Trends Endocrinol. Metabol., 4, 62-69.
- Dantzer, R. & Kelley, K.W. (1989). Stress and immunity: An integrated view of relationships between the brain and the immune system. Life Sci., 44, 1995-2008.
- Darko, D. F., Gillin, J. C., Risch, S. C., et al. (1989). Mitogen-stimulated lymphocyte proliferation and pituitary hormones in major depression. Biol. Psychiatry, 26, 145-155.
- Darko, D. F., Irwin, M. R., Risch, C., & Gillin, J. C. (1991). Plasma beta-endorphin and natural killer cell activity in major depression: A preliminary study. Psychiat. Res., 43, 111-119.
- Darko, D. F., Lucas, A. H., & Gillin, J. C. (1986). Replication of lower lymphocyte blastogenesis in depression. Am. J. Psychiatry, 143, 1492-1493.

- Darko, D. F., Lucas, A. H., Gillin, J. C. et al. (1988). Cellular immunity and the hypothalamic pituitary axis in major depressive disorder: A preliminary study. Psychiat. Res., **25**, 1-9.
- Darko, D. F., Wilson, N. W., Golshan, S., & Gillin, J. C. (1991). A critical appraisal of mitogen-induced lymphocyte proliferation in depression. Am. J. Psychiatry, **148**, 337-344.
- De Goeij, D. C. E., Binnekade, R., & Tilders, F. J. H. (1992a). Chronic stress enhances vasopressin but not corticotropin-releasing factor secretion during hypoglycemia. Am. J. Physiol., **263**, E394-E399.
- De Goeij, D. C. E., Dijkstra, H., & Tilders, F. J. H. (1992b). Chronic psychosocial stress enhances vasopressin, but not corticotropin-releasing factor, in the external zone of the median eminence of male rats: relationship to subordinate status. Endocrinology, **131**, 847-853.
- De Goeij, D. C. E., Jezova, D., & Tilders, F. J. H. (1992c). Repeated stress enhances vasopressin synthesis in corticotropin releasing factor neurons in the paraventricular nucleus. Brain Res., **577**, 165-168.
- De Goeij, D. C. E., Kvetnansky, R., Whitnall, M. H., Jezova, D., Berkenbosch, F., & Tilders, F. J. H. (1991). Repeated stress-induced activation of corticotropin-releasing factor neurons enhances vasopressin stores and colocalization with corticotropin-releasing factor in the median eminence of rats. Neuroendocrinology, **53**, 150-159.
- de Kloet, E. R. (1991). Brain corticosteroid receptor balance and homeostatic control. Front. Neuroendocrinol., **12**, 95-164.
- de Kloet, E. R., & Reul, J. M. H. (1987). Feedback action and tonic influence of corticosteroids on brain function: A concept arising from heterogeneity of brain receptor systems. Psychoneuroendocrinology, **12**, 83-105.

- Delahanty, D. L., Dougall, A. L., Craig, K. J., Jenkins, F. J., & Baum, A. (1997). Chronic stress and natural killer cell activity after exposure to traumatic death. Psychosom. Med., 59, 467-476.
- Deinzer, R., Kirschbaum, C., Gresele, C., & Hellhammer, D. H. (1997). Adrenocortical responses to repeated parachute jumping and subsequent h-CRH challenge in experienced healthy subjects. Physiol. Behav., 61, 507-511.
- Dhabhar, F. S., Miller, A. H., McEwen, B. S., et al. (1996). Effects of stress on immune cell distribution: Dynamic and hormonal mechanisms. J. Immunology, 154, 5511-5527.
- Dinan, T. G. (1994). Glucocorticoids and the genesis of depressive illness: A psychobiological model. Br. J. Psychiatry, 164, 365-371.
- Dorian, B., Garfinkel, P., Brown, G., Shore, A., Gladman, D., & Keystone, E. (1982). Aberrations in lymphocyte subpopulations and function during psychological stress. Clin. exp. Immunol., 50, 132-138.
- Draca, S. (1995). Prolactin as an immunoreactive agent. Immunol. Cell Biol., 73, 481-483.
- Dugue, B., Leppanen, E. A., Teppo, A. M., Fyhrquist, F., & Grasbeck, R. (1993). Effects of psychological stress on plasma interleukins-1 beta and 6, C-reactive protein, tumour necrosis factor alpha, anti-diuretic hormone and serum cortisol. Scand. J. Clin. Lab Invest., 53, 555-561.
- Duman, R. S., Heninger, G. R., & Nestler, E. J. (1997). A molecular and cellular theory of depression. Arch. Gen. Psychiatry, 54, 596-606.
- Dunn, A. J. (1990). Interleukin-1 as a stimulator of hormone secretion. Prog. Neuro. Endocrin. Immunol., 3, 26-34.
- Dunn, A. J. (1993). Infection as a stressor: A cytokine-mediated activation of the pituitary-adrenal axis? In C. F. Symposium (Ed.), Corticotropin-Releasing Factor, 172 (pp. 226-242). Wiley, Chichester:

- Dunn, A. J. (1995). Interactions between the nervous system and the immune system. In F. E. Bloom & D. J. Kupfer (Eds.), Psychopharmacology: The Fourth Generation of Progress (pp. 719-731). New York: Raven Press.
- Dyck, D. G., & Greenberg, A. H. (1991). Immunopharmacological tolerance as a conditioned response: Dissecting the brain-immune pathways. In R. Ader, D. S. Felten, & N. Cohen (Eds.), Psychoneuroimmunology (pp. 663-684). San Diego: Academic.
- Dyck, D. G., Janz, L., Osachuk, T. A. G., Falk, J., Labinsky, J., & Greenberg, A. H. (1990). The Pavlovian conditioning of IL-1-induced glucocorticoid secretion. Brain Behav. Immun., 4, 93-104.
- Evans, D. L., Folds, J. D., Petitto, J. M., Golden, R. N., Pedersen, C. A., Corrigan, M., Gilmore, J. H., Silva, S. G., Quade, D., & Ozer, H. (1992). Circulating natural killer cell phenotypes in men and women with major depression: Relation to cytotoxic activity and severity of depression. Arch. Gen. Psychiatry, 49, 388-395.
- Evans, D. L., Leserman, J., Perkins, D. O., Stern, R. A., Murphy, C., Tamul, K., Liao, D., van der Horst, C. M., Hall, C. D., Folds, J. D., Golden, R. N., & Petitto, J. M. (1995). Stress-associated reductions of cytotoxic T lymphocytes and natural killer cells in asymptomatic HIV infection. Am. J. Psychiatry, 152, 543-550.
- Evans, D. L., Pederson, C. A., & Folds, J. D. (1988). Major depression and immunity: Preliminary evidence of natural killer cell populations. Prog. Neuro-psychopharm. Biol. Psychiatry, 12, 739-748.
- Esterling, B. A., Kiecolt-Glaser, J. K., Bodnar, J. C., & Glaser, R. (1994). Chronic stress, social support, and persistent alterations in the natural killer cell response to cytokine in older adults. Health Psychol., 13, 291-298.
- Esterling, B. A., Kiecolt-Glaser, J. K., & Glaser, R. (1996). Psychosocial modulation of cytokine-induced natural killer cell activity in older adults. Psychosom. Med., 58, 264-272.

- Fenz W. D. (1988). Learning to anticipate stressful events. J. Sport & Exercise Psychol., 10, 223-228.
- Fu, T. K., Jarvik, L. F., Yen, F. S., & Matsuyama, S. S. (1977). In vitro effect of imipramine proliferation of human leukocytes. Arch. Gen. Psychiat., 34, 728-730.
- Fujiwara, R. & Orita, K. (1987). The enhancement of the immune response by pain stimulation in mice: I. The enhancement effect on PFC production via sympathetic nervous system *in vivo* and *in vitro*. J. Immunol., 138, 3699-3703.
- Futterman, A. D., Kemeny, M. E., Shapiro, D., & Fahey, J. L. (1994). Immunological and physiological changes associated with induced positive and negative mood. Psychosom. Med., 56, 499-511.
- Glaser, R., Pearl, D. K., Kiecolt-Glaser, J. K., & Malarkey, W. B. (1994). Plasma cortisol levels and reactivation of latent Epstein-Barr virus in response to examination stress. Psychoneuroendocrinology, 19, 765-772.
- Glaser, R., Pearson, G. R., Bonneau, R. H., Esterling, B. A., Atkinson, C., & Kiecolt-Glaser, J. K. (1993). Stress and the memory T-cell response to the Epstein-Barr virus in healthy medical students. Health Psychol., 12, 435-442.
- Glaser, R., Rice, J., Speicher, C. E., Stout, J. C., & Kiecolt-Glaser, J. K. (1986). Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity. Behav Neurosci, 100, 675-678.
- Gold, P. W., Licinio, J., Wong, M. L., & Chrousos, G. P. (1995). Corticotropin releasing hormone in the pathophysiology of melancholic and atypical depression and in the mechanism of action of antidepressant drugs. Ann. N.Y. Acad. Sci., 771, 716-729.
- Goodkin, K., Blaney, N. T., Feaster, D., Fletcher, M. A., Baum, M. K., Mantero-Atienza, E., Klimas, N. G., Millon, C., Szapocznik, J., & Eisdorfer, C. (1992). Active coping style is associated with natural killer cell cytotoxicity in asymptomatic HIV-1 seropositive homosexual men. J. Psychosom. Res., 36, 635-650.

- Griffiths, J., Ravindran, A. V., Merali, Z., & Anisman, H. (1996). Immune and behavioral correlates of typical and atypical depression. Soc. Neurosci. Abst., 22, 1350.
- Griffiths, J., Ravindran, A. V., Merali, Z., & Anisman, H. (1997). Neuroendocrine measures and lymphocyte subsets in depressive illness: Influence of a clinical interview concerning life experiences. Psychoneuroendocrinology, 22, 225-236.
- Guy, W. (1976). ECDEU assessment manual for psychopharmacology. Bethesda, MD: National Institute for Mental Health, Psychopharmacology Research Branch.
- Halbreich, U., Asnis, G., Shindeldecker, R., Zumoff, B., & Nathan, S. (1985). Cortisol secretion in endogenous depression. Arch. Gen. Psychiatry, 42, 904-914.
- Halvorsen, R., & Vassend, O. (1987). Effects of examination stress on some cellular immunity functions. J. Psychosom. Res., 31, 693-701.
- Hamilton, M. (1959). The assessment of anxiety states by rating. Br. J. Med. Psychol., 32, 50-55.
- Hamilton, M. (1967). Development of a rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol., 32, 50-55.
- Henry, J.P. (1993). Biological basis of the stress response. NIPS, 8, 69-73.
- Herbert, T. B., & Cohen, S. (1993). Depression and immunity: A meta-analytic review. Psychol. Bull., 113, 472-486.
- Herbert, T. B., Coriell, M. & Cohen, S. (1994). Analysis of lymphocyte proliferation data: Do different approaches yield the same results? Brain. Behav. Immun., 8, 153-162.
- Herman, J. P., & Culligan, W. E. (1997). Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends in Neurosci., 20, 78-83.
- Hickie, I., Hickie, C., Lloyd, A. et al. (1993). Impaired *in vivo* immune responses in patients with melancholia. Br. J. Psychiatry, 162, 651-657.
- Hoffman-Goetz, L., & Pedersen, B. K. (1994). Exercise and the immune system: a model of the stress response? Immunology Today, 15, 382-387.

- Holsboer, F. (1992). The hypothalamic-pituitary-adrenocortical system. In E. S. Paykel (Eds.), Handbook of Affective Disorders (pp. 267-287). New York: Guilford Press.
- Holsboer, F. (1995). Neuroendocrinology of mood disorders. In F. E. Bloom & D. J. Kupfer (Eds.), Psychopharmacology: The Fourth Generation of Progress (pp. 957-970). New York: Raven Press.
- Hopkins, S. J., & Rothwell, N. J. (1995). Cytokines and the nervous system II: Actions and mechanisms of action. Trends in the Neurosciences, 18, 130-136.
- Howland, R. H., & Thase, M. E. (1991). Biological studies of dysthymia. Biol. Psychiatry, 30, 283-304.
- Howland, R. H., & Thase, M. E. (1995). Biological processes in Depression: An updated review and integration. In E. E. Beckham & W.R. Leber (Eds.), Handbook of Depression, 2nd Ed. (pp. 213-279). New York: Guildford Press.
- Huberty, C. J. & Morris, J. D. (1989). Multivariate analysis versus univariate analyses. Psych. Bull., 105, 302-308.
- Ironson, G., Wynings, C., Schneiderman, N., Baum, A., Rodriguez, M., Greenwood, D., Benight, C., Antoni, M., LaPerriere, A., Huang, H.-S., Klimas, N., & Fletcher, M. A. (1997). Posttraumatic stress symptoms, intrusive thoughts, loss, and immune function after Hurricane Andrew. Psychosom. Med., 59, 128-141.
- Irwin, M., Brown, M., Patterson, T., Hauger, R., Mascovich, A., & Grant, I. (1992). Neuropeptide Y and natural killer cell activity: Findings in depression and Alzheimer's caregiver stress. FASEB J., 5, 3100-3107.
- Irwin, M., Caldwell, C., Smith, T. L., Brown, S., Schuckit, M. A., & Gillin, J. C. (1990a). Major depressive disorder, alcoholism, and reduced natural killer cell cytotoxicity. Arch. Gen. Psychiatry, 47, 713-719.
- Irwin, M., Daniels, M., Smith, T. L., Bloom, E., & Weiner, H. (1987). Impaired natural killer cell activity during bereavement. Brain. Behav. Immun., 1, 98-104.

- Irwin, M., Patterson, T., Smith, T. L., Caldwell, C., Brown, S. A., Gillin, J. C., & Grant, I. (1990b). Reduction of immune function in life stress and depression. Biol. Psychiatry, 27, 22-30.
- Irwin, M., Smith, T. L., & Gillin, J. C. (1987). Low natural killer cytotoxicity in major depression. Life Sci., 41, 2127-2133.
- Irwin, M. R., Smith, T. L., & Gillin, J. C. (1992). Electroencephalographic sleep and natural killer cell activity in depressed patients and control subjects. Psychosom. Med., 54, 10-21.
- Jabaaij, L., Hattum, J. V., Vingerhoets, A. J. J. M., Oostveen, F. G., Duivenvoorden, H. J., & Ballieux, R. E. (1996). Modulation of the immune response to rDNA hepatitis B vaccination by psychological stress. J. Psychosom. Res., 41, 129-137.
- Jurcovicova, J., Krueger, K. S., & Royta, R. (1997). Effect of glycosylated and non-glycosylated prolactin on the proliferation of normal human lymphocytes. Physiol. Res., 46, 199-201.
- Kamen-Siegel, L., Rodin, J., Seligman, M. E. P., & Dwyer, J. (1991). Explanatory style and cell-mediated immunity in elderly men and women. Health Psychol., 10, 229-235.
- Kanner, A. D., Coyne, J. C., Schaefer, C., & Lazarus, R. S. (1981). Comparison of two modes of stress measurement: daily hassles and uplifts versus major life events. J. Behav. Med., 4, 1-39.
- Kang, D.-H., Coe, C. L., & McCarthy, D. O. (1996). Academic examinations significantly impact immune responses, but not lung function, in healthy and well-managed asthmatic adolescents. Brain. Behav. Immun., 10, 164-181.
- Kang, D.-H., Coe, C. L., McCarthy, D. O. & Ershler, W. B. (1997). Immune responses to final examinations in healthy and asthmatic adolescents. Nurs. Res., 46, 12-19.
- Kessler, R. C., Price, R. H., & Wortman, C. B. (1985). Social factors in psychopathology: Stress, social support and coping processes. Ann. Rev. Psychol., 36, 531-572.

- Kiecolt-Glaser, J. K., Dura, J. R., Speicher, C. E., Trask, O. J., & Glaser, R. (1991). Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. Psychosom. Med., 53, 345-362.
- Kiecolt-Glaser, J. K., Garner, W., Speicher, C. E., Penn, G., & Glaser, R. (1984). Psychosocial modifiers of immunocompetence in medical students. Psychosom. Med., 46, 7-14.
- Kiecolt-Glaser, J. K., & Glaser, R. (1991). Stress and immune function in humans. In R. Ader, D. L. Felten, & N. Cohen (Eds.), Psychoneuroendocrinology (pp. 849-867). San Diego: Academic Press.
- Kiecolt-Glaser, J. K., & Glaser, R. (1995). Psychoneuroimmunology and health consequences: Data and shared mechanisms. Psychosom. Med., 57, 269-274.
- Kiecolt-Glaser, J. K., Glaser, R., Gravenstein, S., Malarkey, W. B., & Sheridan, J. (1996). Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc. Natl. Acad. Sci. USA, 93, 3043-3047.
- Kiecolt-Glaser, J. K., Glaser, R., Shuttleworth, E. C., Dyer, C. S., Ogrocki, P., & Speicher, C. E. (1987). Chronic stress and immunity in family caregivers of Alzheimer's disease victims. Psychosom. Med., 49, 523-535.
- Kiecolt-Glaser, J. K., Glaser, R., Williger, D., Stout, J., Messick, G., Sheppard, S., Ricker, D., Romisher, S. C., Briner, W., Bonnell, G., & Donnerberg, R. (1985). Psychosocial enhancement of immunocompetence in a geriatric population. Health Psychol., 4, 25-41.
- Kiecolt-Glaser, J. K., Kennedy, S., Malkoff, S., Fisher, L., Speicher, C. E., & Glaser, R. (1988). Marital discord and immunity in males. Psychosom. Med., 50, 213-229.
- Kiecolt-Glaser, J. K., Malarkey, W. B., Cacioppo, J. T., & Glaser, R. (1994). Stressful personal relationships: Immune and endocrine function. In R. Glaser & J. K. Kiecolt-Glaser (Eds.), Handbook of Stress and Immunity (pp. 321-339). San Diego, CA: Academic Press.

- Kiecolt-Glaser, J. K., Malarkey, W. B., Chee, M., Newton, T., Cacioppo, J. T., Mao, H., & Glaser, R. (1993). Negative behavior during marital conflict is associated with immunological down-regulation. Psychosom. Med., 55, 395-409.
- Kirschbaum, C., & Hellhammer, D. H. (1994). Saliva cortisol in psychoneuroendocrine research: Recent developments and applications. Psychoneuroendocrinology, 19, 313-333.
- Kirschbaum, C., Pirke, K.M., & Hellhammer, D. H. (1993). The "Trier Social Stress Test" - A tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology, 28, 76-81.
- Kizaki, T., Oh-Ishi, S., & Ohno, H. (1996). Acute cold stress induces suppressor macrophages in mice. J. Appl. Physiol., 81, 393-399.
- Kizaki, T., Oh-Ishi, S., Ookawara, T., Yamamoto, M., Izawa, T., & Ohno, H. (1996). Glucocorticoid mediated generation of suppressor macrophages with high density FcγRII during acute cold stress. Endocrinology, 137, 4260-4267.
- Klein, D. F. (1990). Depressive personality: Reliability, validity, and relation to dysthymia. J. Abn. Psychol., 4, 412-421.
- Knapp, P. H., Levy, E. M., Giorgi, R. G., Black, P. H., Fox, B. H., & Heeren, T. C. (1992). Short-term immunological effects of induced emotion. Psychosom. Med., 54, 133-148.
- Knudsen, J. H., Courtpayen, M., Kjaersgaard, E., & Christensen, N. J. (1995). Lymphocyte subset composition in peripheral-blood from normal subjects may be influenced by both spleen size and plasma norepinephrine. Scand. J. Clin. Lab. Invest., 55, 634-648.
- Kohn, P. M., Hay, B. D., & Legere, J. J. (1994). Hassles, coping styles, and negative well-being. Pers. Individ. Diff., 17, 169-179.
- Kronfol, Z., & House, J. D. (1984). Depression, cortisol, and immune function. Lancet, 1026-1027.

- Kronfol, Z., Nair, M., Goodson, J., et al. (1989). Natural killer cell activity in depressive illness: Preliminary report. Biol. Psychiatry, 26, 753-756.
- Kronfol, Z., Nair, M., Zhang, Q., Hill, E. E., & Brown, M. B. (1997). Circadian immune measures in healthy volunteers: Relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom. Med., 59, 42-50.
- Kronfol, Z., Sylva, J., Greden, J., et al. (1982). Cell-mediated immunity in melancholia. Psychosom. Med., 44, 304-307.
- Kronfol, Z., Sylva, J., Greden, J., Dembinsky, S., Gardner, R., & Carroll, B. (1983). Impaired lymphocyte function in depressive illness. Life Sciences, 33, 241-247.
- Laudenslager, M. L., Ryan, S. M., Drugan, R. C., & Hyson, R. L. (1983). Coping and immunosuppression: Inescapable but not escapable shock suppresses lymphocyte proliferation. Science, 221, 568-570.
- Lazarus, R. S. (1993). Coping theory and research: Past, present, and future. Psychosom. Med., 55, 243-247.
- Larzelere, R. E. & Mulaik S. A. (1977). Simple-sample test for many correlations. Psych. Bull., 84, 557-569.
- Levy, S. M., Fernstrom, J., Herberman, R. B., et al. (1991). Persistently low natural killer cell activity and circulating levels of plasma beta-endorphin: Risk factors for infectious disease. Life Sci., 48, 107-116.
- Lloyd, C. (1980). Life events and depressive disorder reviewed: II. Events as precipitating factors. Arch. Gen. Psychiatry, 37, 541-548.
- Lovallo, L. R., Pincomb, G. A., Edwards, G. L., Brackett, D. L., & Wilson, M. F. (1986). Work pressure and type A behavioral pattern exam stress in male medical students. Psychosom. Med., 48, 125-133.
- Lu, L. (1994). University transition: major and minor life stressors, personality characteristics and mental health. Psychol. Med., 24, 81-87.

- Lupien, S. J., Gaudreau, S., Tchiteya, B. M., Maheu, F., Sharma, S., Nair, N. P. V., Hauger, R. L., McEwen, B. S., & Meaney, M. J. (1997). Stress-induced declarative memory impairment in health elderly subjects: Relationship to cortisol reactivity. J. Clin. Endocrinol. Metab., 82, 2070-2075.
- Lysle, D. T., Cunnick, J. E., & Rabin, B. S. (1990). Stressor-induced alteration of lymphocyte proliferation in mice: Evidence for enhancement of mitogenic responsiveness. Brain. Behav. Immun., 4, 269-277.
- Maes, M. (1995). Evidence for an immune response in major depression: A review and a hypothesis. Prog. Neuropsychopharmacol. Biol. Psychiatry, 19, 11-38.
- Maes, M., Bosmans, E., DeJongh, R., Kenis, G., Vandoolaeghe, E., & Neels, H. (1997). Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment-resistant depression. Cytokine, 9, 853-858.
- Maes, M., Bosmans, E., Meltzer, H. Y., Scharpe, S., & Suy, E. (1993). Interleukin-1 β : A putative mediator of HPA axis hyperactivity in major depression? Am. J. Psychiatry, 150, 1189-1193.
- Maes, M., Bosmans, E., & Meltzer, H. Y. (1995a). Immunoendocrine aspects of major depression. Relationships between plasma interleukin-6 and soluble interleukin-2 receptors, prolactin and cortisol. Eur. Arch. Psychiatry Clin. Neurosci., 245, 172-178.
- Maes, M., Bosmans, E., Suy, E., Vandervorst, C., Dejonckheere, C., Minner, B., & Raus, J. (1991a). Depression-related disturbances in mitogen-induced lymphocyte responses, interleukin-1b and soluble interleukin-2 receptor production. Acta Psychiatr. Scand., 84, 379-386.
- Maes, M., Lambrechts, J., Bosmans, E., Jacobs, J., Suy, E., Vandervorst, C., Dejonckheere, C., Minner, B., & Raus, J. (1992). Evidence for a systemic immune activation during depression: Results of leukocyte enumeration by flow cytometry in conjunction with monoclonal antibody staining. Psychol. Med., 22, 45-53.

- Maes, M., Lambrechts, J., Suy, E., Vandervorst, C., & Bosmans, E. (1994). Absolute number and percentage of circulating natural killer, non-MHC-restricted T cytotoxic, and phagocytic cells in unipolar depression. Biol. Psychiatry, 29, 157-163.
- Maes, M., Meltzer, H. Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., & Desnyder, R. (1995b). Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J. Affect. Disord., 34, 301-309.
- Maes, M., Song, C., Lin, A. H., et al., (1998). The effects of psychological stress on humans - Increased production of pro-inflammatory cytokines and a TH1-like response in stress-induced anxiety. Cytokine, 10, 313-318.
- Maes, M., Stevens, W., Peeters, D., DeClerk, L., Scharpe, S., Bridts, C., Schotte, C., & Cosyns, P. (1991b). A study on the blunted natural killer cell activity in severely depressed patients. Life Sci., 50, 505-513.
- Maes, M., Vandoolaeghe, E., Ranjan, R., Bosmans, E., Bergmans, R., & Desnyder, R. (1995c). Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J. Affect. Disord., 36, 29-36.
- Maes, M., Vandoolaeghe, E., Vanhunsel, F., Bril, T., Demedts, P., Wauters, A., & Neels, H. (1997). Immune disturbances in treatment-resistant depression - modulation by antidepressant treatments. Hum. Psychopharm. Clin. Exp., 12, 153-162.
- Maier, S. F., Watkins, L. R., & Fleshner, M. (1994). Psychoneuroimmunology. The interface between behavior, brain and immunity. Am. Psychol., 49, 1004-1017.
- Manuck, S. B., Cohen, S., Rabin, B. S., Muldoon, M. F., & Bachen, E. A. (1991). Individual differences in cellular immune response to stress. Psychol. Sci., 2, 111-115.

- Marsland, A. L., Manuck, S. B., Fazzari, T. V., Stewart, C. J., & Rabin, B. S. (1995). Stability of individual differences in cellular immune responses to acute psychological stress. Psychosom. Med., 57, 295-298.
- Matthews, K. A., Caggiula, A. R., McAllister, C. G., Berga, S. L., Owens, J. F., Flory, J. D., & Miller, A. L. (1995). Sympathetic reactivity to acute stress and immune response in women. Psychosom. Med., 57, 564-571.
- McAdams, C., & Leonard, B. E. (1993). Neutrophil and monocyte phagocytosis in depressed patients. Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 17, 971-984.
- McCoy, J., Carey, J., & Krause, J. (1990). Quality control in flow cytometry for diagnostic laboratory procedures. Am. J. Clin. Pathol., 93, S27-S37.
- McEwen, B. (1995). Neuroendocrine interactions. In F. E. Bloom & D. J. Kupfer (Eds.), Psychopharmacology: The Fourth Generation of Progress (pp. 705-718). New York: Raven Press.
- McKinnon, W., Weisse, C. S., Reynolds, C. P., Bowes, C. A., & Baum, A. (1989). Chronic stress, leukocyte subpopulations, and humoral response to latent viruses. Health Psychol., 8, 389-402.
- Meaney, M. J., Diorio, J., Francis, D., Widdowson, J., LaPlante, P., Caldji, C., Sharma, S., Seckl, J. R., & Plotsky, P. M. (1996). Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress. Dev. Neurosci., 18, 49-72.
- Merali, Z., Lacosta, S., & Anisman, H. (1997). Effects of interleukin-1 β and mild stress on alterations of norepinephrine, dopamine and serotonin neurotransmission: a regional microdialysis study. Brain Res., 761, 225-235.
- Miller, A. H., Spencer, R. L., McEwen, B. S., & Stein, M. (1993). Depression, adrenal steroids, and the immune system. Ann. Med., 25, 481-487.
- Mohl, P. C., Huang, L., Bowden, C., et al. (1987). Natural killer cell activity in major depression. Am. J. Psychiatry, 144, 1619.

- Monroe, S. M., & Depue, R. A. (1991). Life stress and depression. In J. Becker & A. Kleinman (Eds.), Psychosocial Aspects of Depression (pp. 101-130). Hillsdale, N.J.: Erlbaum.
- Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. Psychol. Bull., 110, 406-425.
- Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. Br. J. Psychiatry, 134, 382-389.
- Muller, N., Hofschuster, E., Ackenheil, M., Mempel, W., & Eckstein, R. (1993). Investigations of the cellular immunity during depression and the free interval: Evidence for an immune activation in affective psychosis. Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 17, 713-730.
- Munck, A., Guyre, P. M., & Holbrook, N. J. (1984). Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocrinol. Rev., 5, 25-44.
- Nakano, K. (1993). Personality, hassles, and psychological well-being. Jap. J. Psychol., 64, 123-127.
- Naliboff, B. D., Benton, D., Solomon, G. F., Morley, J. E., Fahey, J. L., Bloom, E. T., Makinodan, T., & Gilmore, S. L. (1991). Immunological changes in young and old adults during brief laboratory stress. Psychosom. Med., 53, 121-132.
- Naliboff, B. D., Solomon, G. F., Gilmore, S. L., Fahey, J. L., Benton, D., & Pine, J. (1995). Rapid changes in cellular immunity following a confrontational role-play stressor. Brain Behav. Immun., 9, 207-219.
- Nemeroff, C. B. (1996). The corticotropin-releasing factor (CRF) hypothesis of depression: New findings and new directions. Mol. Psychiatry, 1, 336-342.

- Nemeroff, C. B., Krishnan, K. R. R., Reed, D., et al. (1992). Adrenal gland enlargement in major depression. A computed tomographic study. Arch Gen Psychiatry, 49, 384-387.
- Nemeroff, C. B., Owens, M. J., Bissette, G., Andom, A. C., & Stanley, M. (1988). Reduced corticotropin-releasing factor binding sites in the frontal cortex of suicide victims. Arch Gen Psychiatry, 45, 577-579.
- Nemeroff, C. B., Widerlov, E., Bissette, G., et al. (1984). Elevated concentrations of CFS corticotropin-releasing factor-like immunoreactivity in depressed patients. Science, 226, 1342-1343.
- O'Leary, A. (1990). Stress, emotion, and human immune function. Psychol. Bull., 108, 363-382.
- Ortega, E. Collazos, M. E. Barriga, C., & De la Fuente, M. (1992). Stimulation of the phagocytic function in guinea pig peritoneal macrophages by physical activity stress. Eur. J. Appl. Physiol., 64, 323-327.
- Ortega, E. Forner, M. A. Barriga, C., & De la Fuente, M. (1993). Effect of age and swimming-induced stress on the phagocytic capacity of peritoneal macrophages from mice. Mech. Aging Dev., 70, 53-63.
- Pariante, C. M. & Miller, A. H. (1995). Natural killer cell activity in major depression: A prospective study of the in vivo effects of desmethylimipramine treatment. Eur. J. Neuropsychopharm. Supp., 83-85.
- Patterson, T. L., Semple, S. J., Temoshok, L. R., Atkinson, J. H., McCutchan, J. A., Straits-Troster, K., Chandler, J. L., Grant, I., & Group, H. N. R. C. (1995). Stress and depressive symptoms prospectively predict immune change among HIV-seropositive men. Psychiatry, 58, 299-312.
- Pavlidis, N., & Chirigos, M. (1980). Stress-induced impairment of macrophage tumoricidal function. Psychosom. Med., 42, 47-54.

- Paykel, E. S., Prusoff, B. A., & Uhlenhuth, E. H. (1971). Scaling of life events. Arch. Gen. Psychiatry, 43, 561-565.
- Paykel, E. S., & Cooper, Z. (1992). Life events and social stress. In E. S. Paykel (Ed.), Handbook of Affective Disorders (pp. 149-170). New York: Guildford Press.
- Paykel, E. S., Myers, J. K., Dienelt, M. N., Klerman, G. L., Lindenthal, J. J., & Pepper, M. P. (1969). Life events and depression: A controlled study. Arch. Gen. Psychiatry, 21, 753-760.
- Pearlin, L. I. & Schooler, C. (1978). The structure of coping. J. Health & Soc. Behav., 19, 2-21.
- Petitto, J. M., Folds, J. D., Ozer, H., Quade, D., & Evans, D. L. (1992). Abnormal diurnal variation in circulating natural killer cell phenotypes and cytotoxic activity in major depression. Am. J. Psychiatry, 149, 694-696.
- Pfohl, B., Sherman, B., Schelchte, J., & Stone, R. (1985). Pituitary-adrenal axis rhythm disturbances in psychiatric depression. Arch Gen Psychiatry, 42, 897-903.
- Phillips, K., Gunderson, J., Hirschfeld, R. M. A., & Smith, L. (1990). A review of the depressive personality. Am. J. Psychiatry, 147, 830-837.
- Pike, J. L., Smith, T. L., Hauger, R. L., Nicassio, P. M., McClintick, J., Costlow, C., & Irwin, M. R. (1997). Chronic life stress alters sympathetic, neuroendocrine and immune responsivity to and acute psychological stressor in humans. Psychosom. Med., 59, 447-457.
- Plotsky, P. M., Owens, M. J., & Nemeroff, C. B. (1995). Neuropeptide alterations in mood disorders. In F. E. Bloom & D. J. Kupfer (Eds.), Psychopharmacology: The Fourth Generation of Progress (pp. 971-982). New York: Raven Press.
- Pruessner, J. C., Gaab, J., Hellhammer, D. H., Lintz, D., Schommer, N., & Kirschbaum, C. (1997). Increasing correlations between personality traits and cortisol stress responses obtained by data aggregation. Psychoneuroendocrinology, 22, 615-625.

- Pruessner, J. C., Wolf, O. T., Hellhammer, D. H., Buske-Kirschbaum, A., von Auer, K., Jobst, S., Kaspers, F., & Kirschbaum, C. (1997). Free cortisol levels after awakening: A reliable biological marker for the assessment of adrenocortical activity. Life Sci. **26**, 2539-2549.
- Raadsheer, F. C., Hoogendijk, W. J. C., Stam, F. C., Tilders, F. J. H., & Swaab, D. F. (1994). Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology, **60**, 436-444.
- Ravindran, A. V., Bialik, R. J., & Lapierre, Y. D. (1994). Primary early onset dysthymia, biochemical correlates of the therapeutic response to fluoxetine: 1. Platelet monoamine oxidase and the dexamethasone test. J. Affect. Disord., **31**, 111-117.
- Ravindran, A. V., Griffiths, J., Merali, Z., & Anisman, H. (1998a). Circulating lymphocyte subsets in major depression and dysthymia with typical or atypical features. Psychosom. Med., **60**, 283-289.
- Ravindran, A. V., Anisman, H., Merali, Z., Charbonneau, Y., Telner, J., Bialik, R. J., Wiens, A., Ellis, J., & Griffiths, J. (1998b). Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: Clinical symptoms and functional impairments. Am. J. Psychiatry, submitted.
- Ravindran, A. V., Griffiths, J., Zaharia, M., Merali, Z., & Anisman, H. (1997a). Immune and endocrine alterations in atypical depression. In: World Congress of Biological Psychiatry, Nice, France.
- Ravindran, A. V., Griffiths, J., Merali, Z., & Anisman, H. (1996a). Primary dysthymia: A study of several psychosocial, endocrine and immune correlates. J. Affect. Disord., **40**, 73-84.
- Ravindran, A. V., Griffiths, J., Merali, Z., & Anisman, H. (1996b). Variations of lymphocyte subsets associated with stress in depressive populations. Psychoneuroendocrinology, **21**, 659-671.

- Ravindran, A. V., Griffiths, J., Merali, Z., & Anisman, H. (1995a). Lymphocyte subsets associated with major depression and dysthymia: Modification by antidepressant treatment. Psychosom. Med., 57, 555-563.
- Ravindran, A. V., Griffiths, J., Waddell, C., & Anisman, H. (1995b). Stressful life events and coping styles in relation to dysthymia and major depressive disorder: Variations associated with alleviation of symptoms following pharmacotherapy. Prog. Neuropsychopharmacol. Biol. Psychiatry, 19, 637-653.
- Ravindran, A. V., Merali, Z., & Anisman, H. (1997). Dysthymia: A biological perspective. In J., Licinio, C. L. Bolis, & P. Gold (Eds.). Dysthymia: From Clinical Neuroscience to Treatment. (pp. 21-44). World Health Organization: Geneva.
- Reber, P. M. (1993). Prolactin and immunomodulation. Am. J. Med., 95, 637-644.
- Reese, D. R., Gross, A. M., Smalley, D. L., & Messer, S. C. (1994). Caregivers of Alzheimer's disease and stroke patients. The Gerontologist, 34, 534-540.
- Revicki, D. A., Turner, R., Brown, R., & Martindale, J. J. (1992). Reliability and validity of a health-related quality of life battery for evaluating outpatient antidepressant treatment. Qual. Life Res., 1, 257-266.
- Rinner, I., Schauenstein, K., Mangge, H., Porta, S., & Kvetnansky, R. (1992). Opposite effects of mild and severe stress on in vitro activation of rat peripheral lymphocytes. Brain, Behav. Immun., 6, 130-140.
- Rocha, H. M. & Ortigasoto, H. A. (1995). Depression in university students of the national school of professional studies in Aragon. Salud Mental, 18, 31-34.
- Ruffin, C. L. (1993). Stress and health: Little hassles vs. major life events. Austral. Psychol., 28, 201-208.
- Russell, D., Peplau, L. A., & Cutrona, C. E. (1980). The revised UCLA Loneliness Scale: Concurrent and discriminant validity evidence. J. Pers. Soc. Psychol., 39, 472-480.
- Rubin, R. T., Phillips, J. J., Sadow, T. F., & McCracken, J. T. (1995). Adrenal gland volume in major depression. Arch. Gen Psychiatry, 52, 213-218.

- Rubin, R. T., Russell, E., Poland, R. E., Lesser, I. M., Winston, R. A., & Blodgett, L. N. (1987). Neuroendocrine aspects of primary endogenous depression. Arch Gen Psychiatry, 44, 328-336.
- Sapolsky, R. M., Armanini, M. P., Packan, D. R., Sutton, S. W., & Plotsky, P. M. (1990). Glucocorticoid feedback inhibition of adrenocorticotrophic hormone secretagogue release. Neuroendocrinology, 51, 328-336.
- Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1986). The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. Endocrine Reviews, 7(3), 284-301.
- Sapolsky, R. M., Rivier, C., Yamamoto, G., Plotsky, P. M., & Vale, W. W. (1987). Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science, 238, 522-524.
- Schedlowski, M., Falk, A., Rohne, A., Wagner, T. O. F., Jacobs, R., Tewes, U., & Schmidt, R. E. (1993). Catecholamines induce alterations of distribution and activity of human natural killer (NK) cells. J. Clin. Immunol., 13, 344-351.
- Schedlowski, M., Hosch, W., Obereck, R., Benschop, R. J., Jacobs, R., Raab, H.-R., & Schmidt, R. E. (1996). Catecholamines modulate human natural killer (NK) cell circulation and function via spleen-independent β 2-adrenergic mechanisms. J. Immunol., 156, 93-99.
- Schedlowski, M., Wichert, D., Wagner, T.O.F. & Tewes, U. (1992). Acute psychological stress increases plasma levels of cortisol, prolactin and TSH. Life Sci., 50, 1201-1205.
- Scheier, M. F., & Bridges, M. W. (1995). Person variables and health: Personality predispositions and acute psychological states as shared determinants for disease. Psychosom. Med., 57, 255-268.
- Scheier, M. F., Matthews, K. A., Owens, J. F., Magovern, G. J., Lefebvre, R. C., et al. (1989). Dispositional optimism and recovery from coronary artery bypass surgery:

the beneficial effects on physical and psychological well-being. J. Pers. Soc. Psychol., 57, 1024-1040.

Schleifer, S. J., Keller, S. E., Bartlett, J. A., Eckholdt, H. M., & Delaney, B. R. (1996). Immunity in young adults with major depressive disorder. Am. J. Psychiatry, 153, 477-482.

Schleifer, S. J., Keller, S. E., Bond, R. N., Cohen, J., & Stein, M. (1989). Major depressive disorder and immunity. Arch. Gen. Psychiatry, 46, 81-87.

Schleifer, S. J., Keller, S. E., Meyerson, A. T., Raskin, M. J., Davis, K. L., & Stein, M. (1984). Lymphocyte function in major depressive disorder. Arch. Gen. Psychiatry, 41, 484-486.

Schmidt, E. D., Janszen, A. W. J. W., Wouterlood, F. G., & Tilders, F. J. H. (1995). Interleukin-1-induced long-lasting changes in hypothalamic corticotropin-releasing hormone (CRH)-neurons and hyperresponsiveness of the hypothalamic-pituitary-adrenal axis. J. Neurosci., 15, 7417-7426.

Seegal, R. F., Brosch, K. O., & Bush, B. (1986). High-performance liquid chromatography of biogenic amines and metabolites in brain, cerebrospinal fluid, urine and plasma. J. of Chromatogr., 377, 131-144.

Seidel, A., Arolt, V., Huntstiger, M., Rink, L., Behnisch, A., & Kirchner, H. (1996a). Increased CD56+ natural killer cells and related cytokines in major depression. Clin. Immunol. & Immunopath., 78, 83-85.

Seidel, A., Arolt, V., Huntstiger, M., Rink, L., Behnisch, A., & Kirchner, H. (1996b). Major depressive disorder is associated with elevated monocyte counts. Acta Psychiatr. Scand., 94, 198-204.

Sgoutas-Emch, S. A., Cacioppo, J. T., Uchino, B. N., Malarkey, W., Pearl, D., Kiecolt-Glaser, J., & Glaser, R. (1994). The effects of an acute psychological stressor on cardiovascular, endocrine, and cellular immune response: A prospective study of individuals high and low in heart rate reactivity. Psychophysiol., 31, 264-271.

- Sheehan, D., Lecrubier, Y., Janavs, J., Knapp, E., Weiller, E., Sheehan, M., Lepine, J. P., & Teherani, M. (1992). Mini-International Neuropsychiatric Interview, Clinician Rated, Version 2.1.
- Shintani, F., Nakaki, T., Kanba, S., Kato, R., & Asai, M. (1995). Role of interleukin-1 in stress responses. Molecular Neurobiology, 10, 47-71.
- Sieber, W. J., Rodin, J., Larson, L., Ortega, S., & Cummings, N. (1992). Modulation of human natural killer cell activity by exposure to uncontrollable stress. Brain Behav. Immun., 6, 141-156.
- Sluzewska, A., Rybakowski, J., Bosmans, E., Sobieska, M., Berghmans, R., Maes, M., & Wiktorowicz, K. (1996). Indicators of immune activation in major depression. Psychiat. Res., 64, 161-167.
- Smith, T. W. (1992). Hostility and health: current status of a psychosomatic hypothesis. Health Psychol., 11, 139-150.
- Smyth, J. M., Ockenfels, M. C., Gorin, A. A., Catley, D., Porter, L. S., Kirschbaum, C., Hellhammer, D. H. & Stone, A., A. (1997). Individual differences in the diurnal cycle of cortisol. Psychoneuroendocrinology, 22, 89-105.
- Spangler, G. (1997). Psychological and physiological responses during an exam and their relation to personality characteristics. Psychoneuroendocrinology, 22, 423-441.
- Spurrell, M. T., & Creed, F. H. (1993). Lymphocyte response in depressed patients and subjects anticipating bereavement. Br. J. Psychiatry, 162, 60-64.
- Stein, M., Miller, A. H., & Trestman, R. L. (1991). Depression, the immune system, and health and illness. Arch. Gen. Psychiatry, 48, 171-177.
- Stokes, P. E., & Sikes, C. R. (1987). Hypothalamic-pituitary-adrenal axis in affective disorders. In H. Y. Meltzer (Eds.), Psychopharmacology: The third generation of progress (pp. 589-608). New York: Raven Press.
- Stone, A. A., Bovbjerg, D. H., Neale, J. M., Napoli, A., Valdimarsdottir, H., Cox, D., Hayden, F. G., & Gwaltney, J. M. (1992). Development of common cold symptoms

- following experimental rhinovirus infection is related to prior stressful events. Behav. Med., **18**, 115-120.
- Stone, A. A., Reed, B. R., & Neale, J. M. (1987). Changes in daily event frequency precede episodes of physical symptoms. J. Hum. Stress, **13**, 70-74.
- Syvalahti, E., Eskola, J., Ruuskanen, O., & Laine, T. (1985). Nonsuppression of cortisol in depression and immune function. Prog. Neuro-Psychopharmacol. Biol. Psychiatry, **9**, 14-22.
- Tabachnick, B. G. & Fidell, L. S. (1989). Using Multivariate Statistics. 2nd Ed. New York: Harper Collins Publishers.
- Tilders, F. J. H., Schmidt, E. D., & De Goeij, D. C. E. (1993). Phenotypic plasticity of CRF neurons during stress. Ann. N.Y. Acad. Sci., **697**, 39-52.
- Tsigos, C., & Chrousos, G. P. (1994). Physiology of the hypothalamic-pituitary-adrenal axis in health and dysregulation in psychiatric and autoimmune disorders. Endocrinol. Metab. Clin. North. Am., **23**, 451-466.
- Uchino, B. N., Cacioppo, J. T., Malarkey, W., & Glaser, R. (1995). Individual differences in cardiac sympathetic control predict endocrine and immune responses to acute psychological stress. J. Pers. Soc. Psych., **69**, 736-743.
- Uehara, A., Gottschall, P. E., Dahl, R. R., & Arimura, A. (1987). Interleukin-1 stimulates ACTH release by an indirect action which requires endogenous corticotropin releasing factor. Endocrinology, **121**, 1580-1582.
- Van Dijken, H. H., De Goeij, D. C. E., Sutanto, W., Mos, J., de Kloet, E. R., & Tilders, F. J. H. (1993). Short inescapable stress produces long-lasting changes in the brain-pituitary-adrenal axis of adult male rats. Neuroendocrinology, **58**, 57-64.
- Van Dijken, H. H., Mos, J., van der Heyden, J. A., & Tilders, F. J. H. (1992). Characterization of stress-induced long-term behavioural changes in rats: evidence in favor of anxiety. Physiol. Behav., **52**, 945-951.

- Weigent, D. A. (1996). Immunoregulatory properties of growth hormone and prolactin. Pharmacol. Ther., 69, 237-257.
- Weiss, D. W., Hirt, R., Tarcic, N., Berzon, Y., Ben-Zur, H., Breznitz, S., Glaser, B., Grover, N. B., Baras, M., & O'Dorisio, T. M. (1996). Studies in psychoneuroimmunology: Psychological, immunological, and neuroendocrinological parameters in Israeli civilians during and after a period of scud missile attacks. Behav. Med., 22, 5-14.
- Weiss J. M., Sundar, S. K., Becker, K. J., & Cierpial, M. A. (1989). Behavioral and neural influences on cellular immune responses: Effects of stress and interleukin-1. J. Clin. Psychiat., 50, 43-55.
- Weisse, C. S. (1992). Depression and immunocompetence: A review of the literature. Psychol. Bull., 111, 475-489.
- Weissman, M. M., & Bothwell, S. (1976). Assessment of social adjustment by patient self-report. Arch. Gen. Psychiatry, 33, 1111-1115.
- Weizman, R., Laor, N., Podliszewski, E., Notti, I., Djaldetti, M., & Bessler, H. (1994). Cytokine production in major depression patients before and after clomipramine treatment. Biol. Psychiatry, 35, 42-47.
- Whitehouse, W. G., Dinges, D. F., Orne, E. C., Keller, S. E., Bates, B. L., Bauer, N. K., Moraham, P., Haupt, B. A., Carlin, M. M., Bloom, P. B., Zaugg, L., & Orne, M. T. (1996). Psychosocial and immune effects of self-hypnosis training for stress management throughout the first semester of medical school. Psychosom. Med., 58, 249-263.
- Wong J. L. & Whitaker, D. J. (1994). The stability and prediction of depressive mood states in college students. J. Clin. Psychol., 50, 715-722.
- Workman, E. A. & La Via, M. F. (1987). T-Lymphocyte polyclonal proliferation and stress response style. Psychol. Rep., 60, 1121-1122.

- Zaharia, M. D., Ravindran, A. V., Griffiths, J., Remington, G. J., Merali, Z., & Anisman, H. (1995). Laboratory and naturalistic stressors influence immune functioning. Soc. Neurosci. Abst., 21, 1396.
- Zalcman, S., Green-Johnson, J., Murray, L., Nance, D. M., Dyck, D., Anisman, H., & Greenberg, A. (1994). Cytokine-specific central monoamine alterations induced by interleukin (IL)-1, IL-2 and IL-6. Brain Res., 643, 90-99.
- Zorrilla, E. P., DeRubeis, R. J. & Redei, E. (1995). High self-esteem and affective stability are associated with higher basal pituitary-adrenal hormone levels. Psychoneuroendocrinology, 20, 591-601.
- Zorrilla, E. P., Redei, E., & DeRubeis, R. J. (1994). Reduced cytokine levels and T-cell function in healthy males: relation to individual differences in subclinical anxiety. Brain. Behav. Immun., 8, 293-312.

Table 1.**Summary of Stressor-Induced Alterations of Enumerative Measures Among Nondepressed Populations.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Dorian, Garfinkel, Brown, Shore, Gladman & Keystone, 1982	4 Male; 4 Female Psychiatry Interns	Final Oral Medical Exam	White Blood Cells	*increased #s
	16 Controls (Psychiatrists; Psychiatry Trainees)	(Chronic)	Absolute Lymphocyte Count	*increased #s
		vs. No Exam: Controls	B-cells	increased #s
				(*high stressed S rel. to control S's)
Kiecolt-Glaser, Kennedy, Malkoff, Fisher, Speicher & Glaser, 1988	32 Separated & 32 Married men	1) Marital separation	CD4 ; CD8, CD4/CD8	no change
		2) Poor marital quality (Chronic)	CD8 CD4+/CD8+	decrease #s decrease ratio
Kiecolt-Glaser, Kennedy, Malkoff, Fisher, Speicher & Glaser, 1988	32 Separated & 32 Married men	1) Marital separation	EBV CVA & EBV HSV-1 titers	Both increase (sep. men)
		2) Poor marital quality	EBV CVA titer EBV HSV-1 titers	no change increase
		(Chronic)		
McKinnon, Weisse, Reynolds, Bowles & Baum, 1989	20 Persons Living Near Damaged TMI nuclear power plant & 20 Controls	uncertainty with previous TMI accident	WBC, Lymphocytes, CD3, T-helper, monocytes, Eosinophils	no change
		(Chronic)	T-suppressor /cytotoxic cell, NK & B-cells	decrease #s
			Neutrophils	increase #s

Table 1 (Continued).**Summary of Stressor-Induced Alterations of Enumerative Measures Among Nondepressed Populations.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Manuck, Cohen, Rabin, Muldoon & Bachen, 1991	25 College Men (subgrouped into High or Low Sympathetic Reactors)	Frustration Stress: Stroop Color-Word Interference Test & Mental Arithmetic (Acute)	CD4, CD19	no change due to stress
			CD8	increase #s (high reactors only)
Knapp, Levy, Giorgi, Black, Fox, Heeren, 1992	Normal Men & Women	Imagined Disturbing & Pleasurable Experiences (Acute)	CD4	slight increase #s
			PMN	increase #s (*with either neg. or pos. emotions)
Sieber, Rodin, Larson, Ortega Cummings, 1992	64 Men: (4 Groups: 1. No Noise; 2. Escapable, 3. Nonescapable, 4. Nonescapable/ Response)	Intermittent Noise Bursts (controllable or uncontrollable) (Acute)	CD4, CD8, CD56	no change
			Total T-cells (CD3)	*decrease #s (*due to decrease trend in CD4 cells) (except in escapable noise group)
Schedlowski et al., 1993	45 Male Tandem Parachute Jumpers	Free-Fall/ Parachute Jump (Acute)	CD2, CD3, CD4, CD8, CD16, CD56 (NK)	*increase #s (immed. after jump)
				*decrease #s (1 hour after jump rel. to baseline)
Brosschot et al., 1994	86 Male Teachers	1) Daily Hassles	CD3, NK cells	more daily hassles = greater decrease #s following task
		2) 8 min. insolvable puzzle & teaching solution to confederate	B cells	increase #s with high daily hassles (control group)

Table 1 (Continued)**Summary of Stressor-Induced Alterations in Enumerative Measures Among Nondepressed Populations.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Futterman, Kemeny, Shapiro, Fahey, 1994	17 Male Actors	Imagined Mood (Valence, Arousal) (Acute)	CD8, CD16, CD56, CD57 cells	increase % (all cond.)
Hoffman-Goetz & Pedersen, 1994	Review	Physical Exercise (Acute)	CD3, CD4, CD8, CD16, CD19, NK, LAK Neutrophils, Leukocytes, Lymphocytes	increase #s (during); decrease #s (after) increase #s decrease #s
Evans et al., 1995	99 HIV+ Asymptomatic & 65 HIV- Homosexual Men	1) HIV+ status 2) life stress assessed by interview (excludes HIV status stress) (Chronic)	CD8+/CD3+; CD8+/CD57+ Cytotoxic T & NK cells with CD57+ NK CD56+	*decrease ratios (both stressors) (*HIV+ only) *decrease (both stressors) (*HIV+ only) *decrease (both stressors) (*HIV+ only)
Matthews et al., 1995	19 Follicular Stage Women; High/Low Sympathetic Reactors	Stroop Test, Public Speech then Star Tracer Task (Acute)	NK, granulocytes, T, B, lymphocytes, monocytes CD4 cells, CD4/CD8	increased #s decrease %
Patterson et al., 1995	63 HIV Seropositive Men	Stressful Life Events (excluding HIV-related) x Depression interaction (Chronic)	CD4 CD8 β 2-microglobulin	decrease no relation increase

Table 1 (Continued).**Summary of Stressor-Induced Alterations of Enumerative Measures
Among Nondepressed Populations.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Zaharia, Ravindran, Griffiths, Remington, & Anisman, 1995	University Students	Academic Examinations	PHA , Con-A- stimulated cell proliferation	increase
	Controls, MDD, Dysthymics	Math Task	PMA-stimulated neutrophil, macrophage activity	no change
		Psychiatric Interview (Acute)	PHA- & Con-A- stimulated cell proliferation	no change
Kang, Coe, McCarthy, 1996	29 Healthy Adolescents,	Academic Examinations	CD4, CD8, CD56 CD16 CD19	increase #s no change decrease #s
	35 Asthmatics	(Acute)	CD4/CD8	increase ratio (*above for both groups)
Kiecolt-Glaser, Glaser, Gravenstein & Malarkey, 1996	32 Chronic Caregivers of Spouses 32 Controls	Chronic Caregiving (Chronic)	CD3, CD4, CD8	no differences
Ironson et al., 1997	180 Persons Living in Areas Affected by Hurricane Andrew 70 Controls	Dealing with Damage/Stress of Hurricane Andrew (Chronic)	CD4, CD8	decreased #s (Hurricane survivors)
			CD56 (NK)	increased #s (Hurricane survivors)
Griffiths, Ravindran, Merali & Anisman, 1997	12 Men, 18 Women (University Students & Hospital Employees)	1) Clinical Interview (either Hassles or Uplifts)	NK	increase #s (after interview & before exam)
		2) Examination (Acute)	CD3, CD4, CD8, CD19	increase #s (exam only)

Table 2.**Summary of Stressor-Induced Alterations of Functional Immune Measures Among Nondepressed Populations.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Dorian, Garfinkel, Brown, Shore, Gladman & Keystone, 1982	4 Male; 4 Female Psychiatry Interns	Final Oral Medical Exam	Con A & PHA-stimulated cell proliferation	*decrease
	16 Controls (Psychiatrists; Psychiatry Trainees)	vs. No Exam: Controls	Plaque-Forming Cell Response	*decrease
		(Chronic?)		*10-14 days prior - High Stress S's;
Clover, Abell, Becker, Crawford & Ramsey, 1989	281 Patients (from 66 Families)	Life Events; Family Satisfaction (APGAR) & Family Cohesion & Adaptability (FACES II)	Influenza B infection development	no relation (Life Events or Family APGAR)
		(Acute/Chronic)		more infections ("Emeshed", "Chaotic" or "Rigid" families)
Manuck, Cohen, Rabin, Muldoon & Bachen, 1991	25 College Men (Subgrouped into High or Low Sympathetic Reactors)	Frustration Stress: Stroop Color-Word Interference Test & Arithmetic	PHA-stimulated cell proliferation	decrease (only among high reactors)
		(Acute)		* sig. neg. rel. with PHA-stimulated cell proliferation
Naliboff et al., 1991	12 Younger Women (21-41 years)	Arithmetic Challenge or No Task	NK cytotoxicity	*increase (*only younger women)
	11 Older Women (65 years+)	(Acute)		** No stress effect on plasma NE, DA, Epi
Bachen et al., 1992	44 Male Undergraduate University Students	Performance of 21-minute Stroop Task or No Task	PHA-stimulated cell proliferation	decrease (post-stress)
		(Acute)		*slight increase among No Task S's with time

Table 2 (Continued).**Summary of Stressor-Induced Alterations of Functional Immune Measures Among Nondepressed Populations.**

Author(s)	Population	Stressor(s)	Immune Measure(s)	Change(s)
Knapp, Levy, Giorgi, Black, Fox, Heeren, 1992	Normal Men & Women	Imagined Disturbing & Pleasurable Experiences (Acute)	PHA-stimulated cell proliferation NK cytotoxicity	decrease (both cond.) weak increase (disturbing condition)
Sieber, Rodin, Larson, Ortega Cummings, 1992	64 Men: (4 Groups: 1. No Noise; 2. Escapable, 3. Nonescapable, 4. Nonescapable/ Response)	Intermittent Noise Bursts: (Controllable or Uncontrollable) (Acute)	NK cytotoxicity	*decrease (Nonescapable/ No Response group only) *optimism & desire to control enhanced above decrease
Stone et al., 1992	17 Undergraduate College Students	1) Life events (LES) 2) Perceived Stress 3) Pos. & Neg. Affect Scale (PANAS) (Acute/Chronic)	Rhinovirus (Cold) Development (after inoculation)	#s Life Events = greater likelihood of cold develop. *No relation with either Perceived Stress or Affect
Glaser et al., 1993	25 EBV Seropositive Medical Students	Academic Examinations (Acute) Perceived Stress /Anxiety	EBV-specific T-cell proliferation EBV-VCA titers	decrease (due to exam) no change
Schedlowski et al., 1993	45 Male Tandem Parachute Jumpers	Free-Fall + 5 Min. Parachute Jump	NK cytotoxicity	*increase (after jump) *decrease (1 hour after jump rel. to baseline)

Table 2 (Continued).**Summary of Stressor-Induced Alterations of Functional Immune Measures Among Nondepressed Populations.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Brosschot et al., 1994	86 Male Teachers	1) Daily Hassles 2) Teaching and Solving an Insolvable Puzzle to Confederate	PHA, PWM-stim. cell proliferation	no change
Futterman, Kemeny, Shapiro, Fahey, 1994	17 Male Actors	Imagined Mood (Valence, Arousal) (Acute)	PHA-stimulated cell proliferation	increase (pos. valence) decrease (neg. valence)
Cacioppo et al., 1995	22 Older Women (56-73 years)	Speech plus Mathematical Challenge (Acute)	PHA & Con A-stim. cell proliferation NK cytotoxicity	decrease (post-stress) *increase (post-stress)
Matthews et al., 1995	19 Follicular Stage Women; (High or Low Sympathetic Reactors)	3 - 3 min. Tasks: Stroop Test Public Speaking Star Tracer (Acute)	PHA, PWM-stimulated cell proliferation NK cell activity	decrease *increase (*high reactors)
Naliboff et al., 1995	20 Male Subjects (no Major Life Events & BDI $\leq$ 11)	Confrontational Role Play or Control Task (Watching Film) (Acute)	NK cytotoxicity	decrease (*adjusted for NK%; post-stress)

Table 2 (Continued).**Summary of Stressor-Induced Alterations of Functional Immune Measures Among Nondepressed Populations.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Uchino, Cacioppo, Malarkey & Glaser, 1995	24 Undergraduate University Women	Arithmetic Challenge	PHA & Con A-stimulated cell proliferation	no change (both groups)
	(classified as High and Low Sympathetic Reactors)	(Acute)	NK cytotoxicity	*increase (after challenge) (*pos. rel. to reactivity)
Christensen et al., 1996	43 Male University Undergraduates (classified as High or Low in Trait Hostility)	Disclosure of either a Personal or Fictitious Stressful Event to Confederate (Acute)	NK cytotoxicity	*increase (*only among High Hostility, Personal Disclosure Group)
Kang, Coe, McCarthy, 1996	29 Healthy Adolescents & 35 Asthmatics	Academic Examinations (Acute)	PHA-stimulated cell proliferation	*increase
			NK cytotoxicity	*decrease
			PMA-stimulated neutrophil activity	*increase (*both groups; exam/post)
Jabaaij et al., 1996	43 Female, 25 Male Students (4 groups: Hi/Lo ESCL x Hi/Lo HSCL)	Psychological stress (HSCL + Everyday Problems Checklist (EPCL)) (Acute/Chronic)	Antibody Levels following Hepatitis B vaccine	no relation *may be vaccine dose-dependent
Kiecolt-Glaser, Glaser, Gravenstein & Malarkey, 1996	32 Chronic Caregivers of Spouses 32 Controls	Chronic Caregiving (Chronic)	Antibody Levels following Fluzone vaccination	decreased (caregivers)

Table 2 (Continued).**Summary of Stressor-Induced Alterations of Functional Immune Measures Among Nondepressed Populations.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Schedlowski et al., 1996	35 Healthy Men (19-36 years) & 10 Splenectomized (7 Male, 3 Female)	Infusion of either: 1) AD or 2) NE	NK cytotoxicity	*increase (AD or NE cond; both groups) * β_2 -adrenergic mediated effect
Weisse et al., 1996	22 Men from Jerusalem (Gulf War Survivors)	Iraqi Scud Missile Attacks in Jerusalem (Chronic?)	NK cytotoxicity; Cell-mediated Lympholysis	increased (during attacks) *anger & anxiety also elevated
Cohen, Line, Manuck, Rabin, Heise & Kaplan, 1997	60 Male Cynomolgus Monkeys	Stable vs. Unstable Social Conditions (15 months) (Chronic)	Development of adenovirus following inoculation	no change *low social status = greater prob. of infection
Ironson et al., 1997	180 Persons Living in Areas Affected by Hurricane Andrew 70 Controls	Dealing with Damage/Stress of Hurricane Andrew (Chronic)	NK cytotoxicity	*decreased (Hurricane survivors) *decrease pos. rel. to onset of new sleep problems

Table 3.**Summary of Enumerative Immune Measure Alterations Associated with Depressive Illness.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)/ Illness</u>	<u>Immune Measure</u>	<u>Change(s)</u>
Irwin, Smith & Gillan, 1987	19 Depressed Men (*10 med-free); 19 controls	Depression	Total Leukocytes, Neutrophils	increase #s (depressed)
			Lymphocytes, Monocytes, Eosinophils	no difference
Irwin, Patterson, Smith, Caldwell, Brown, Gillin & Grant, 1990	50 Controls 19 Alcoholics 9 Alcoholics with Depression 18 Major Depressives 26 Major Depressives (with Past Alcoholism)	Depression and/or Alcoholism	Total WBC , Neutrophils	increase #s (patient groups)
			Lymphocytes, Monocytes	increase #s (alcoholics & alcoholics with depression)
Irwin, Patterson, Smith, Caldwell, Brown, Gillin & Grant, 1990	36 Depressed Hosp. Men	Depression; Stressful Life Events (Psychiatric Epidemiological Research Interview)	Total Leukocytes Neutrophils	increase #s (depressed)
	36 Control Men		Lymphocytes	increase #s (high stress /depressed group)
			Monocytes	no change
Charles, Machowski, Brohee, Wilmotte & Kennes, 1992	26 Major Depressives	Depression; Anxiety (as measures by HAM-A)	CD3, CD4, CD8, CD16 (NK), CD20	no relationship (HAM-A totals)
			CD4/CD8 ratio	*sig. pos. rel. (HAM-A totals) (* only in DST nonsuppressors)

Table 3 (Continued).**Summary of Enumerative Immune Measure Alterations Associated with Depressive Illness.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)/ Illness</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Evans et al., 1992	44 Major Depressives	Depression	CD16 (NK)	decrease #s sig. negative relation with HAM-D scores)
	48 Controls		HNK-1 (large granular lymphocytes)	decrease #s *above only observed in depressed men;
Maes et al., 1992a	28 Minor Depressives	Depression (subtypes) vs. No Illness	*HLADR+, CD19	increased #s (depressed)
	51 Simple Major Depressives		*HLADR+, CD21	increased % (depressed)
	27 Major Depressives with Melancholia 19 Controls		CD19, CD21 *(all B-cell subtypes)	increased #s, % (respectively; melancholics only)
Maes et al., 1992b	38 Hosp. Depressives (mixed types)	Depression vs. No Illness	CD3, CD4, CD8, CD19	increase #s (major depress.)
	10 controls		T-virgin; memory cells; monocytes	increase #s (all depressed)
			CD4/CD8 ratio	increase (minor; simple major dep.)
Petito, Folds, Ozer, Quade & Evans, 1992	24 Major Depressives 24 Controls	Depression vs. No Illness	CD16 (NK) cell (diurnal variations in #s)	no change in depressives decrease in controls
Muller et al., 1993	23 Major Depressives (during episode)	Depressive Episode vs. Remission & No Illness	CD3, CD4, CD4/CD8 ratio	increased % (all depressed S's)
	14 Depressives (in remission) 51 Controls		CD8	no differences

Table 3 (Continued).**Summary of Enumerative Immune Measure Alterations Associated with Depressive Illness.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)</u>	<u>Immune Measures</u>	<u>Change(s)</u>
Maes, Lambrechts, Suy, Vandervorst & Bosmans, 1994	20 Minor Depressives 29 Simple Major Depressives 30 Major Depressives with Melancholia 17 Controls	Depression (subtypes) vs. No Illness	Total Leukocytes Monocytes, Neutrophils	increased #s & % (due to monocytes, neutrophils)
			CD16, CD56 (NK), CTL (non-MHC-restricted T-cytotoxic cells)	*no differences (decrease in NKCA is not rel. to decreased #s or % of NK cells)
Ravindran, Griffiths, Merali & Anisman, 1995	20 Dysthymics 18 Major Depressives 17 Controls	Depression vs. No Illness;	CD3, CD4, CD8, CD19, CD4/CD8 ratio	no differences
		Depressed Patients: 8 week SSRI Treatment	CD16/56 (NK)	*increased #s (depressed groups) (* SSRIs = NK decreased #s: more time required among dysthymics)
Seidel et al., 1996a	27 Hosp. Major Depressives 20 Controls	Depression vs. No Illness	CD16/CD56+ (NK cells)	increased #s & %
Seidel et al., 1996b	33 Hosp. Major Depressives 44 Controls	Depression vs. No Illness	Leukocytes, Monocytes	*increased #s (*pos. treat. response: decline in monocytes)
			CD4, CD8, CD19, CD4/45RO+ (memory cells)	no differences

Table 3 (Continued).**Summary of Enumerative Immune Measure Alterations Associated with Depressive Illness.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)/ Illness</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Griffiths, Ravindran, Merali & Anisman, 1996	31 Dysthymics 18 Major Depressives 23 Controls	Depression vs. No Illness; Arithmetic Challenge (Acute)	NK cells	increased #s (all groups; post- stress)
Griffiths, Ravindran, Merali & Anisman, 1997	18 Major Depressives, 24 Dysthymics, 30 Controls	1) Depression Type (baseline)	NK cells	increase #s (in MDD rel. to controls)
			Lymphocytes, CD8	decrease #s (in Dysth. rel. to controls)
Ravindran, Griffiths, Merali & Anisman, 1997	72 Dysthymics 58 Controls	2) Clinical Interview (either Hassles or Uplifts)	NK cells	increase #s (in both groups due to interview)
		1) Depression severity (MADRAS; (dysth.; BDI controls)	Depression Severity	pos. related to hassle severity w/ severity of depression (both groups)
		2. Hassle Severity	NK cells	*neg. rel. to hassle severity in controls only)

Table 4.**Summary of Functional Immune Measure Alterations Associated with Depressive Illness.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)/ Illness</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Irwin, Smith & Gillan, 1987	19 Depressed Men (*10 medication-free); 19 controls	Depression	NK cytotoxicity	decrease (depressed)
Irwin, Patterson, Smith, Caldwell, Brown, Gillin & Grant, 1990a	50 Controls 19 Alcoholics 9 Alcoholics with Depression 18 Major Depressives 26 Major Depressives (with Past Alcoholism)	Depression and/or Alcoholism	NK cytotoxicity	decrease in all patient groups *dual diagnosis patients further decrease
Irwin, Patterson, Smith, Caldwell, Brown, Gillin & Grant, 1990b	36 Hosp. Depressed Men, 36 Control Men	Depression; Stressful Life Events (Psychiatric Epidemiological Research Interview)	NK cytotoxicity	decrease (both high stress controls & depressives)
Darko, Irwin, Risch, Gillin, 1991	14 Major Depressives (6 -Probable Prev. Hypomanic Episode) 14 Matched Controls	Depression vs. No Illness	NK cytotoxicity	*decrease (depressives) (*pos. rel. to plasma levels β -endorphin)
Maes et al, 1991b	8 Minor Depressives 18 Simple Major Depression 11 Major Depression with Melancholia 13 Controls	Depression (subtypes) vs. No Illness	NK cytotoxicity	*decrease (*sig. only among melancholics)

Table 4 (Continued).**Summary of Functional Immune Measure Alterations Associated with Depressive Illness.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)/ Illness</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Evans et al., 1992	44 Major Depressives (28 Men, 19 Women); 48 Controls (29 Men, 19 Women)	Depression vs. No Illness	NK cytotoxicity	*decrease (depress. men) *NOT rel. to HAM-D scores
Petito, Folds, Ozer, Quade & Evans, 1992	24 Major Depressives, 24 Controls	Depression vs. No Illness	NK cytotoxicity (diurnal variations in activity)	sig. less diurnal variation among major depressives
Hickie, Hickie, Lloyd, Silove & Wakefield, 1993	26 Major Depressives, 31 Major Depressives with Melancholia 57 Controls	Depression vs. No Illness	*Delayed-Type Hypersensitivity (DTH) Skin Responses (*cell-mediated in vivo measure) PHA-stimulated cell proliferation	*abnormal (melancholics) (*not rel. to age, hosp., weight loss or depression severity) no differences
McAdams & Leonard, 1993	20 Major Depressives 8 Bipolars (Manic Phase) 10 Schizophrenics 30 Matched Controls	*Presence of Psychiatric Illness vs. No Illness (* Psychiatric S's tested prior to and after 6-8 weeks treatment)	Monocyte Phagocytosis (zymosan-stimulated) Neutrophil Phagocytosis (zymosan-stimulated) PHA-stimulated cell proliferation	increased (baseline: Manic & Depressed S's; post-treat. Manic, Schizophrenics) decreased (post-treat.: Depressed) decreased: (psychiat. groups) no differences (post-treat.) decreased (baseline & post-treat. Depressed)

Table 4 (Continued).**Summary of Functional Immune Measure Alterations Associated with Depressive Illness.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)/ Illness</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Muller et al., 1993	23 Major Depressives (during episode)	Depressive Episode vs. Remission & No Illness	Diphtheria- & Tetanus- stimulated-cell proliferation	decreased (depressed S's)
	14 Depressives (in remission)		PWM- & PHA- stimulated	decreased
	51 Controls		suppressor cell activity	
Spurrell & Creed, 1993	10 Major Depressives 8 Spouses of Severely Ill 9 Controls	Depression, Anticipation of Bereavement or No Illness	Lymphocyte Activity (Ratio of PHA- stimulated cell counts to control cell counts)	*neg. rel. to depression scores (*Depressed S's) *pos. rel. to depression scores (*S's Anticipating Bereavement)

Table 4 (Continued).**Summary of Functional Immune Measure Alterations Associated with Depressive Illness.**

<u>Author(s)</u>	<u>Population</u>	<u>Stressor(s)/ Illness</u>	<u>Immune Measure(s)</u>	<u>Change(s)</u>
Bauer et al., 1995a	27 Unipolar Major Depressives 27 Controls	Depression vs. No Illness	NK cytotoxicity	decreased (depressed S's)
			Con A, PHA, PWM-stimulated cell proliferation	no differences
			titers (IgA, IgG, IgM)	no differences
Pariante & Miller, 1995	15 Major Depressives (4 men, 11 women) 8 Controls (2 men, 6 women)	Depression vs. No Illness	NK cytotoxicity:	
		1) Baseline	1) Baseline	increased (depressed S's)
		2) 12 weeks TCA Treatment (desmethylimi- pramine)	2) 12 weeks TCA Treatment	*no differences (rel. to controls) *treatment nonresponders: decreased (rel. to responders)

Table 5.**Cytokine Alterations Associated with Stressors & Depressive Illness.**

<u>Author(s)</u>	<u>Pop.</u>	<u>Stress or Behavioral Measure(s)</u>	<u>Cytokine Measure(s)</u>	<u>Results</u>
Maes et al., 1992	38 Hosp. Depressives (mixed types) 10 controls	Depression	IL-2 receptors (CD25+ cells)	increased #s (major depress. only)
Dugue, Leppanen, Teppo, Fyhrquist & Grasbeck, 1993	7 Men (Stroop Test) 9 Men, 6 Women (Parachute Jump)	1) Stroop Color Test QR 2) Novice Parachute Jump (Acute)	IL-1, IL-6 (ADH, C-reactive protein also meas.)	no change with either stressor *pos. relation between IL-1 and ADH (parachute stress only)
Maes, Bosmans, Meltzer, Scharpe & Suy, 1993	19 Hosp. Major Depressives 9 Hosp. Minor Depressives 10 Controls	Depression vs. No Illness	IL-1 β (supernatants from mitogen-stimulated cultures)	*increased levels (depressed) (*sig. pos. rel. to post-DST values)
Weizman et al., 1994	10 Major Depressives 10 Matched Controls	Depression vs. No Illness	IL-1, IL-2 & IL-3-like activity (supernatants from mitogen-stimulated cultures)	*decreased levels (untreated depressives) (*IL-1 β & IL-3 increased after drug treatment)
Bauer et al., 1995b	7 Major Depressives with Melancholia	Administration of Endotoxin-Containing Drug to Depressives	Plasma IL-1, IL-6 & TNF- α	*increased levels (several hours after endotoxin) (*increases associated with suppressed REM & better mood)
Maes, Bosmans & Meltzer, 1995(a)	13 Hosp. Major Depressives 11 Schizophrenics	Depression, Schizophrenia vs. No Illness	Plasma IL-1 β & IL-6 receptors Plasma IL-2 receptors	*no differences (small IL-6 increase schizo.) increased levels (both hosp. groups)

Table 5 (Continued).**Cytokine Alterations Associated with Stressors & Depressive Illness.**

<u>Author(s)</u>	<u>Pop.</u>	<u>Stress or Behavioral Measure(s)</u>	<u>Cytokine Measure(s)</u>	<u>Results</u>
Maes et al., 1995c	21 Minor, 25 Simple Major, 25 Melancholic Depressives	Depression vs. No illness	serum IL-1 receptor antagonist (IL-1ra)	*increased levels *pos. rel. to illness severity; unrelated to HPA activity **women higher levels than men
Seidel et al., 1996a	39 Hosp. Major Depressives 39 Matched Controls	*Depression vs. No Illness (*Depression examined during & after acute clinical stage)	sIL-2 receptors IL-1 β , IL-2, IL-6, IL-10, IFN- γ (supernatants from mitogen-stimulated cultures)	*increased levels (depressed; in mitogen-stim. cultures only) *increased levels (depressed)
Griffiths, Ravindran, Merali & Anisman, 1996	31 Dysthymics 18 Major Depressives 23 Controls	Depression vs. No Illness *classified as "Typical "or "Atypical"	serum (non-stimulated) IL-1	*increased (atypical major depressives) (* S's also show elevated plasma ACTH)
Kiecolt-Glaser, Glaser, Gravenstein & Malarkey, 1996	32 Chronic Caregivers of Spouses 32 Controls	Chronic Caregiving (Chronic)	IL-1 β , IL-2 IL-6 (production from PBMC)	*decreased levels (caregivers) *no change (*prior to and following Fluzone vaccination)

Table 5 (Continued).**Cytokine Alterations Associated with Stressors & Depressive Illness.**

<u>Author(s)</u>	<u>Pop.</u>	<u>Stress or Behavioral Measure(s)</u>	<u>Cytokine Measure(s)</u>	<u>Results</u>
Sluzewska et al., 1996	49 Hosp. Major Depressives 15 Matched Controls	Depression vs. No Illness	Plasma IL-6 Plasma sIL-2R, sIL-6R (receptors)	increased levels (depressed) increased conc. (depressed)
Anisman et al., 1998, submitted	14 Typical & 31 Atypical Major Depressives; 14 Typical & 15 Atypical Dysthymics 27 Control Subjects	Depression vs. No Illness	IL-1 β production (from PHA-Stimulated Lymphocyte cultures) IL-2 production (from PHA-Stimulated Lymphocyte cultures)	*increased (dysthymics with either typical or atypical features) *pos. rel. to age of onset & illness duration **increased (all depressed groups) **pos. rel. to conc. plasma NE

Table 6.

Mean Basal Plasma Norepinephrine, Epinephrine, ACTH, Cortisol & Prolactin for All Subjects Participating in Experiments 1, 2, & 3.

<u>Plasma Endocrine Measure</u>	<u>Mean</u>	<u>SD</u>	<u>SEM</u>
Norepinephrine (pg/ml)	480.44	117.15	13.18
Epinephrine (pg/ml)	215.15	82.35	9.15
ACTH (pg/ml)	60.01	31.59	2.40
Cortisol (ug/dl)	16.37	8.45	0.89
Prolactin (ug/L)	17.48	9.51	0.73

Table 7.

Mean Basal [H]³ Con A- & PHA-Stimulated Cell Proliferation (c.p.m.) as well as PMA-Stimulated Macrophage & Neutrophil Activity (r.l.u.) for All Subjects Participating in Experiments 1, 2, & 3.

<u>Functional Immune Measure</u>	<u>Mean</u>	<u>SD</u>	<u>SEM</u>
Con A-Stimulated Lymphocyte Proliferation (dose/well)			
1.0 ug/well	28.7 x 10 ³	16.0 x 10 ³	1.33 x 10 ³
2.0 ug/well	37.8 x 10 ³	20.2 x 10 ³	1.68 x 10 ³
5.0 ug/well	133.3 x 10 ³	31.7 x 10 ³	2.64 x 10 ³
PHA-Stimulated Lymphocyte Proliferation (dose/well)			
0.625 ug/well	34.1 x 10 ³	25.0 x 10 ³	2.16 x 10 ³
1.25 ug/well	59.3 x 10 ³	33.6 x 10 ³	2.91 x 10 ³
2.50 ug/well	87.4 x 10 ³	41.9 x 10 ³	3.64 x 10 ³
Macrophage Activity	2.46 x 10 ⁵	2.44 x 10 ⁵	3.21 x 10 ⁴
Neutrophil Activity	7.83 x 10 ⁶	4.33 x 10 ⁶	5.79 x 10 ⁵

Table 8.

Mean Scores for the Beck Depression Inventory, Perceived Stress Scale, UCLA Loneliness Scale, Life Events Scale, Daily Hassles & Uplifts Scale & the Coping Strategies Scale for All Subjects Participating in Experiments 1, 2, & 3.

<u>Behavioral Measure</u>	<u>Mean</u>	<u>SD</u>	<u>SEM</u>
Beck Depression Inventory	4.65	4.93	0.38
Perceived Stress Scale	25.52	8.77	0.68
UCLA Loneliness Scale	36.07	10.60	0.83
Life Events Scale - Frequency	7.61	4.81	0.37
- Intensity	82.85	54.14	4.17
Daily Hassles Scale - Frequency	29.81	26.41	2.04
- Severity	45.97	45.60	3.53
Daily Uplifts Scale - Frequency	51.60	34.45	2.67
- Intensity	97.60	72.21	5.59
Coping Strategies Scale:			
1) Emotional Expression plus Social Support Seeking	39.92	8.90	0.70
2) Emotional Containment plus Passivity	39.36	11.19	0.88
3) Individual Coping plus Cognitive Restructuring	48.04	8.78	0.69

Table 9A.

Mean Scores for the Beck Depression Inventory, Perceived Stress Scale, UCLA Loneliness Scale, Life Events Scale, Daily Hassles & Uplifts Scale & the Coping Strategies Scale for Male Subjects with Low, Moderate or High Beck Depression Inventory Classifications.

<u>Behavioral Measure</u>	<u>BDI Class.</u>	<u>Mean</u>	<u>SD</u>	<u>SEM</u>
Beck Depression Inventory	Low	0.79	0.99	0.14
	Moderate	5.44	1.96	0.39
	High	13.00	2.00	0.50
Perceived Stress Scale	Low	19.15	6.68	0.93
	Moderate	27.08	7.36	1.48
	High	32.27	6.98	1.80
UCLA Loneliness Scale	Low	30.55	7.56	1.06
	Moderate	42.76	9.98	2.00
	High	46.25	9.63	0.50
Life Events Scale -Frequency	Low	6.81	5.02	0.69
	Moderate	9.28	4.61	0.92
	High	10.68	6.95	1.65
Life Events Scale - Intensity	Low	72.42	55.13	7.57
	Moderate	100.00	51.75	10.35
	High	116.56	73.91	18.48
Daily Hassles - Frequency	Low	28.15	32.18	4.46
	Moderate	32.78	22.49	4.50
	High	35.44	26.99	6.75
Daily Hassles - Severity	Low	42.83	62.15	8.62
	Moderate	48.96	27.83	5.57
	High	58.06	46.34	11.59

Table 9A (Continued).

Mean Scores for the Beck Depression Inventory, Perceived Stress Scale, UCLA Loneliness Scale, Life Events Scale, Daily Hassles & Uplifts Scale & the Coping Strategies Scale for Male Subjects with Low, Moderate or High Beck Depression Inventory Classifications.

<u>Behavioral Measure</u>	<u>BDI Class.</u>	<u>Mean</u>	<u>SD</u>	<u>SEM.</u>
Daily Uplifts - Frequency	Low	55.60	51.73	5.23
	Moderate	53.12	36.18	7.36
	High	43.00	38.44	9.61
Daily Uplifts - Intensity	Low	110.14	81.17	11.26
	Moderate	98.16	73.44	14.69
	High	81.63	80.77	20.19
Coping Strategies Scale:				
1) Emotional Expression plus Social Support Seeking	Low	35.40	7.29	1.03
	Moderate	42.92	7.57	1.54
	High	44.45	10.34	2.67
2) Emotional Containment plus Passivity	Low	34.95	10.51	1.49
	Moderate	44.06	7.58	1.55
	High	51.74	10.03	2.60
3) Individual Coping plus Cognitive Restructuring	Low	48.66	9.92	1.40
	Moderate	47.39	9.57	1.95
	High	51.73	10.08	2.60

Table 9B.

Mean Scores for the Beck Depression Inventory, Perceived Stress Scale, UCLA Loneliness Scale, Life Events Scale, Daily Hassles & Uplifts Scale & the Coping Strategies Scale for Female Subjects with Low, Moderate or High Beck Depression Inventory Classifications.

<u>Behavioral Measure</u>	<u>BDI Class.</u>	<u>Mean</u>	<u>SD</u>	<u>SEM.</u>
Beck Depression Inventory	Low	1.18	1.25	0.14
	Moderate	5.26	1.73	0.40
	High	13.15	3.00	0.69
Perceived Stress Scale	Low	21.44	6.72	0.85
	Moderate	31.06	5.05	1.19
	High	36.61	6.09	1.44
UCLA Loneliness Scale	Low	31.74	8.77	1.11
	Moderate	36.35	6.54	1.59
	High	42.56	11.32	2.67
Life Events Scale -Frequency	Low	6.75	4.25	0.54
	Moderate	6.17	3.02	0.71
	High	9.11	4.84	1.15
Life Events Scale - Intensity	Low	72.73	47.15	5.94
	Moderate	69.04	36.76	8.66
	High	105.78	58.09	13.69
Daily Hassles - Frequency	Low	24.87	25.69	3.24
	Moderate	24.28	10.49	2.47
	High	43.89	32.77	7.72
Daily Hassles - Severity	Low	36.79	50.73	6.39
	Moderate	38.22	17.32	4.08
	High	77.22	49.96	11.77

Table 9B (Continued).

Mean Scores for the Beck Depression Inventory, Perceived Stress Scale, UCLA Loneliness Scale, Life Events Scale, Daily Hassles & Uplifts Scale & the Coping Strategies Scale for Female Subjects with Low, Moderate or High Beck Depression Inventory Classifications

<u>Behavioral Measure</u>	<u>BDI Class.</u>	<u>Mean</u>	<u>SD</u>	<u>SEM.</u>
Daily Uplifts - Frequency	Low	52.27	30.69	3.87
	Moderate	47.44	34.33	5.73
	High	50.44	40.16	9.47
Daily Uplifts - Intensity	Low	99.79	67.42	8.50
	Moderate	99.33	68.85	9.16
	High	95.94	77.63	18.30
Coping Strategies Scale:				
1) Emotional Expression plus Social Support Seeking	Low	36.22	6.89	0.88
	Moderate	41.89	8.90	2.09
	High	47.95	8.70	2.05
2) Emotional Containment plus Passivity	Low	34.24	10.53	1.35
	Moderate	40.13	8.82	2.08
	High	43.09	10.26	2.42
3) Individual Coping plus Cognitive Restructuring	Low	47.49	8.83	1.07
	Moderate	45.68	6.69	1.58
	High	45.75	9.53	2.25

Table 10A.

Mean Battelle Quality of Life Subscale Scores of Male Subjects with Low, Moderate or High Beck Depression Inventory Classifications.

<u>Behavioral Measure</u>	<u>BDI Class.</u>	<u>Mean</u>	<u>SD</u>	<u>SEM.</u>
General Health	Low	4.23	0.63	0.10
	Moderate	3.80	0.60	0.18
	High	2.89	0.78	0.26
Health Perception	Low	85.80	12.33	1.97
	Moderate	77.61	21.69	5.60
	High	57.66	24.35	8.12
Energy	Low	72.34	15.33	2.24
	Moderate	57.47	18.49	4.24
	High	39.65	19.14	5.77
Concentration	Low	77.09	15.77	2.30
	Moderate	63.48	12.66	2.91
	High	56.82	9.82	2.96
Alertness	Low	4.99	10.23	1.49
	Moderate	24.31	23.07	2.62
	High	32.54	23.48	7.08
Social Interaction (Low score = Higher Quality)	Low	20.86	16.64	2.43
	Moderate	32.15	16.86	3.97
	High	39.98	15.47	4.66
Life Satisfaction	Low	5.85	0.83	0.12
	Moderate	4.79	1.13	0.26
	High	3.64	1.20	0.36

Table 10B.

**Mean Battelle Quality of Life Subscale Scores of Female Subjects
with Low, Moderate or High Beck Depression Inventory Classifications.**

<u>Behavioral Measure</u>	<u>BDI Class.</u>	<u>Mean</u>	<u>SD</u>	<u>SEM.</u>
General Health	Low	3.97	0.64	0.10
	Moderate	3.31	1.03	0.29
	High	3.00	0.84	0.26
Health Perception	Low	80.87	16.97	2.48
	Moderate	57.95	27.60	7.65
	High	57.37	22.71	6.84
Energy	Low	68.22	18.19	2.45
	Moderate	50.75	21.25	5.31
	High	39.39	17.03	4.73
Concentration	Low	81.02	12.15	1.64
	Moderate	64.69	15.11	3.78
	High	54.00	13.83	3.84
Alertness	Low	5.70	9.27	1.64
	Moderate	24.31	23.07	5.76
	High	42.56	18.86	5.23
Social Interaction (Low score = Higher Quality)	Low	18.93	18.01	2.43
	Moderate	27.63	14.47	3.62
	High	41.86	18.96	5.26
Life Satisfaction	Low	5.80	0.83	0.11
	Moderate	4.50	0.90	0.22
	High	2.85	1.28	0.36

Table 11.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Basal Plasma ACTH Concentrations.

<i>Criterion Measure:</i>				
<u>Basal Plasma ACTH</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One:				
BDI	.074	-.486	-.074	.005
Step Two:				.
Severity of Hassles	-.381**	-.562**	-.486**	.145**

** $p < .01$

Table 12.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Emotional Expression Plus Social Support Seeking Scores & Emotional Containment Plus Passivity Scores on Basal Plasma Cortisol Concentrations.

<i>Criterion Measure:</i>				
<u>Basal Plasma Cortisol</u>	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr²</i>
Step One:				
BDI	-.061	-.111	-.062	.004
Step Two:				
Emotional Expression plus				
Social Support Seeking	.271	.359*	.338*	.084*
Step Three:				
Emotional Containment +	-.150	-.228*	-.291*	.063*
Passivity				

* $p < .05$

Table 13.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Emotional Containment Plus Passivity Scores on Basal Plasma Prolactin Concentrations.

<u>Criterion Measure:</u>				
<u>Basal Plasma Prolactin</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One:				
BDI	-.048	-.092	-.048	.002
Step Two:				
Emotional Containment + Passivity	.170	.176*	.209*	.035*

* $p < .05$

Table 14A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Social Interaction, & Life Satisfaction Scores on Basal Plasma Cortisol Concentrations.

<i>Criterion Measure:</i>				
<u>Basal Plasma Cortisol</u>	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr²</i>
Step One:				
BDI	-.100	-.012	-.006	.012
Step Two:				
Social Interaction	-.231	-.118*	-.279*	.053*
Step Three:				
Life Satisfaction	-.121	-.820*	-.320*	.096*

Table 14B.

Multiple Regression Analysis for the Effects of Beck Depression Inventory (BDI), Social Interaction, & Life Satisfaction Scores on Basal Plasma Cortisol Concentrations.

[$R^2 = .10$, $F(3, 82) = 2.92$, $p < .05$].

<i>Criterion Measure:</i>				
<u>Basal Plasma Cortisol</u>	<i>r</i>	<i>b</i>	<i>β</i>	<i>t</i>
BDI	-.100	-.14	-.08	.45
Social Interaction	-.231	-.11*	-.27*	2.04*
Life Satisfaction	-.121	-1.82*	-.32*	2.00*

* $p < .05$

Table 14C.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Social Interaction, & Life Satisfaction Scores on Basal Plasma Prolactin Concentrations.

<i>Criterion Measure:</i>				
<u>Basal Plasma Prolactin</u>	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr²</i>
Step One:				
BDI	-.03	-.07	-.03	.001
Step Two:				
Social Interaction	-.20	-.11*	-.27*	.060*
Step Three:				
Life Satisfaction	-.19	-2.21*	-.30*	.050*

* $p < .05$

Note: Multiple regression analyses showed both Social Interaction and Life Satisfaction to be negatively associated with changes in basal plasma prolactin levels [$R^2=.10$, $F(3, 139) = 5.24$, $p < .01$].

Table 15A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Basal Plasma Cortisol Concentrations on Basal 2.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u>				
<u>Basal Lymphocyte Proliferation</u>				
<u>(2.0 ug Con A)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr²</u>
Step One:				
BDI	-.029	-114.87	-.029	.001
Step Two:				
Basal Plasma Cortisol	.29	486.74*	.245*	.061*

* $p < .05$

Table 15B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Basal Plasma Cortisol Concentrations on Basal 5.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u>				
<u>Basal Lymphocyte Proliferation</u>				
<u>(5.0 ug Con A)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr²</u>
Step One:				
BDI	.137	1018.126	.137	.019
Step Two:				
Basal Plasma Cortisol	.24*	958.323*	.258*	.085*

* $p < .05$

Table 16A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Basal Plasma Cortisol Concentrations on Basal 1.25 ug PHA-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u>				
<u>Basal Lymphocyte Proliferation</u>				
<u>(1.25 ug PHA)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr²</u>
Step One:				
BDI	.09	729.927	.09	.008
Step Two:				
Cortisol Concentrations	.22*	1158.907*	.285*	.089*

* p < .05

Table 16B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Basal Plasma Cortisol Levels on Basal 2.5 ug PHA-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u>				
<u>Basal Lymphocyte Proliferation</u>				
<u>(2.5 ug PHA)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr²</u>
Step One:				
BDI	.16	1692.478	.16	.026
Step Two:				
Cortisol Levels	.25*	1860.741*	.352*	.150*

* p < .05

Table 17A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Emotional Expression Plus Social Support Seeking on Basal 1.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(1.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	.016	49.788	.016	.000
Step Two: Emot Exp. + Soc. Sup.	.19	358.81*	.206*	.034*

Table 17B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Emotional Expression and Social Support Seeking, & Individual Coping Plus Cognitive Restructuring Scores on Basal 2.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(2.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	-.008	-31.06	-.008	.000
Step Two: Emot. Exp. + Soc. Sup.	.19	516.66*	.231*	.042*
Step Three: Individual Coping	-.20	-464.38*	-.203*	.077*

Table 17C.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Emotional Expression Plus Social Support Seeking on Basal 5.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(5.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	.020	483.65	.082	.007
Step Two: Emot. Exp. + Soc. Sup.	.20	645.37	.194	.036

* $p < .05$

Table 18A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Plasma Cortisol & Individual Coping Plus Cognitive Restructuring Scores on Basal 2.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(2.0 ug Con A)</u>				
	r	b	β	sr^2
Step One: BDI	.001	3.08	.001	.000
Step Two: Plasma Cortisol	.25*	486.42	.243	.063*
Step Three: Individual Coping plus Cognitive Restructuring	-.19	-525.29*	-.270*	.073*

Table 18B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores, Plasma Cortisol & Individual Coping Plus Cognitive Restructuring Scores on Basal 5.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(5.0 ug Con A)</u>				
	r	b	β	sr^2
Step One: BDI	.15	1091.13	.15	.022
Step Two: Plasma Cortisol	.26*	1024.93	.280*	.079*
Step Three: Individual Coping plus Cognitive Restructuring	-.12	-915.33*	-.247*	.076*

* $p < .05$

Table 19A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Life Satisfaction Scores on Basal 1.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(5.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	.054	182.596	.054	.003
Step Two: Life Satisfaction	-.12	-3525.82*	-.319*	.050*

Table 19B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Life Satisfaction Scores on Basal 2.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(2.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	.07	313.6	.070	.005
Step Two: Life Satisfaction	-.18	-4237.93*	-.289*	.044**

Table 19C.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Life Satisfaction Scores on Basal 5.0 ug Con A-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(5.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	.106	749.575	.106	.011
Step Two: Life Satisfaction	-.23	-7331.459*	-.315*	.059*

* $p < .05$

** $p < .01$

Table 20A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on Basal 0.625 ug PHA-Stimulated Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(0.625 ug PHA)</u>				
	r	b	β	sr^2
Step One: BDI	.096	546.525	.096	.009
Step Two: Energy	.20	276.43	.219	.040

Table 20B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on Basal 1.25 ug PHA-Stimulated Basal Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(1.25 ug PHA)</u>				
	r	b	β	sr^2
Step One: BDI	.158	1171.28	.158	.025
Step Two: Energy	.142	398.97*	.240*	.063*

Table 20C.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on 2.5 ug PHA-Stimulated Basal Lymphocyte Proliferation.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(2.5 ug PHA)</u>				
	r	b	β	sr^2
Step One: BDI	.235*	2222.44	.235*	.055*
Step Two: Energy	.15	263.59	.126	.066*

* $p < .05$

Table 21.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on Basal Neutrophil Activity.

<u>Criterion Measure:</u>				
<u>Basal Neutrophil Activity</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One:				
BDI	.229	206067.10	.229	.052
Step Two:				
Energy	.32	100152.75*	.468*	.243*

* $p < .05$

Table 22A

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & *Absolute* Change of Plasma Prolactin Levels on *Absolute* Change of 1.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u><i>Criterion Measure:</i></u> <u><i>Absolute Change of</i></u> <u><i>Lymphocyte Proliferation</i></u> <u><i>(1.0 ug Con A)</i></u>	<i>r</i>	<i>b</i>	β	sr^2
Step One: BDI	-.114	-429.661	-.114	.013
Step Two: <i>Absolute</i> Change of Prolactin Levels	.450*	858.56*	.472*	.221*

Table 22B

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & *Absolute* Change of Plasma Prolactin Levels on *Absolute* Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u><i>Criterion Measure:</i></u> <u><i>Absolute Change of</i></u> <u><i>Lymphocyte Proliferation</i></u> <u><i>(2.0 ug Con A)</i></u>	<i>r</i>	<i>b</i>	β	sr^2
Step One: BDI	-.209	-1074.20	-.209	.044
Step Two: <i>Absolute</i> Change of Prolactin Levels	.353*	1080.37*	.474*	.250*

Table 22C

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & *Absolute* Change of Plasma Prolactin Levels on *Absolute* Change of 5.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u><i>Criterion Measure:</i></u> <u><i>Absolute Change of</i></u> <u><i>Lymphocyte Proliferation</i></u> <u><i>(5.0 ug Con A)</i></u>	<i>r</i>	<i>b</i>	β	sr^2
Step One: BDI	-.141	-930.81	-.141	.020
Step Two: <i>Absolute</i> Change of Prolactin Levels	.198	769.38	.263	.083

* $p < .05$

Table 23A

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Percentage Change of Plasma Cortisol Concentrations Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Plasma Cortisol</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr²</u>
Step One:				
BDI	.103	1.604	.103	.011
Step Two:				
Severity of Hassles	**-.256	-.868	**-.461	** .156

** p < .01

Note: Simple regression analyses showed specific major life events (Exits from the Social Field) were negatively associated with percentage changes in plasma cortisol levels ($r = -.33$).

Table 23B

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Percentage Change of Plasma Prolactin Concentrations Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Plasma Prolactin</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr²</u>
Step One:				
BDI	.233	3.46	.233	.054
Step Two:				
Severity of Hassles	-.214	-1.01	**-.435	** .197

** p < .01

Table 24.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Emotional Expression Plus Social Support Seeking on Percentage Change of Plasma Prolactin Levels Prior to an Introductory Psychology Examination.

<i>Criterion Measure:</i>				
<u>% Change of Plasma Prolactin</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One:				
BDI	.132	1.90	.132	.017
Step Two:				
Emotional Expression + Social Support Seeking	-.204*	-3.4*	-.414*	.133*

* $p < .05$

Note: Multiple regression analyses found that BDI and use of Emotional Expression plus Social Support Seeking accounted for 14% of the variance in changes of plasma prolactin levels ($R^2 = .14$; $F(2, 43) = 3.30$, $p < .05$).

Table 25.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Percentage Change of Plasma Epinephrine Levels Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u>				
<u>% Change of</u>				
<u>Plasma Epinephrine</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr²</u>
Step One:				
BDI	0.07	0.74	0.07	.01
Step Two:				
Severity of Hassles	*-0.29	**-.062	**-.044	**0.14

* p < .05

** p < .01

Table 26.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Perceived Stress on Percentage Change of Plasma Norepinephrine Levels Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u>				
<u>% Change of Plasma Norepinephrine</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One:				
BDI	0.09	0.90	0.09	.01
Step Two:				
Perceived Stress	*0.32	2.78	**0.54	** 0.14

* $p < .05$

** $p < .01$

Table 27A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 1.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u> <u>Lymphocyte Proliferation</u> <u>(1.0 ug Con A)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	-.10	-1.97	-.10	.011
Step Two: Intensity of Major Life Events.	-.23	-.59	-.29	*.08

Table 27B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 2.0 ug Con-A Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u> <u>Lymphocyte Proliferation</u> <u>(2.0 ug Con A)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	-.05	-.80	-.05	.00
Step Two: Intensity of Major Life Events	.23	.50	.30	*.09

Table 27C.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 5.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u> <u>Basal Lymphocyte Proliferation</u> <u>(5.0 ug Con A)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	-.17	-4.8	-.17	0.03
Step Two: Intensity of Major Life Events	.12	-0.25	0.1	.01

* $p < .05$

Table 28.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Satisfaction Scores on *Absolute* Change of Plasma Epinephrine Immediately Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u>				
<u>Absolute Change of Plasma</u>				
<u>Epinephrine</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One:				
BDI	.16	3.16	.16	.03
Step Two:				
Life Satisfaction	.08	29.88	.48*	.10*

* $p < .05$

Multiple regression analyses showed that BDI and Life Satisfaction accounted for 12 % of the variance in changes of plasma Epi, $R^2 = .12$; $F(2, 52) = 3.59$, $p < .05$.

Table 29.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) & Quality of Life Energy Scores on *Absolute* Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation Immediately Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u>				
<u>Absolute Change of 2.0 ug</u>				
<u>Con A-Stimulated Cell</u>				
<u>Proliferation</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr²</u>
Step One:				
BDI	.03	135.613	.03	.00
Step Two: Energy	.28	*389.90	*.45	*.11

* $p < .05$

Table 30A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Percentage Change of Plasma Prolactin Levels on Percentage Change of 1.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(1.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	-.10	-1.95	-.10	.01
Step Two: Percentage Change of Plasma Prolactin Levels	*.48	1.65	** .51	** .25

Table 30B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Percentage Change of Plasma Prolactin Levels on Percentage Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(2.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	-.23	-4.12	-0.23	.05
Step Two: Percentage Change of Plasma Prolactin Level	.25	*.86	*.30	*.08

Table 30C.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Percentage Change of Plasma Prolactin Levels on Percentage Change of 5.0 ug Con A-Stimulated Lymphocyte Proliferation Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(5.0 ug Con A)</u>				
	<i>r</i>	<i>b</i>	<i>β</i>	<i>sr</i>²
Step One: BDI	-.07	-1.18	-.08	.01
Step Two: Percentage Change of Plasma Prolactin Level	.38	*1.02	*.40	*.15

* $p < .05$

Table 31.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Severity of Hassles on Percentage Change of Plasma Prolactin Levels Prior to an Introductory Psychology Examination.

<u>Criterion Measure:</u>				
<u>% Change of</u>				
<u>Plasma Prolactin</u>	r	b	β	sr^2
Step One:				
BDI	.133	.65	.13	.020
Step Two:				
Severity of Hassles	*.51	.96	*.54	*.24

* $p < .05$

Table 32A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 0.625 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Midterm Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(0.625 ug PHA)</u>	r	b	β	sr^2
Step One: BDI	*-.39	*-2.98	*-.39	*.15
Step Two: Intensity of Life Events	-.55	-.55	*-.50	*.24

Table 32B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 1.25 ug PHA-Stimulated Lymphocyte Proliferation Prior to a Midterm Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(1.25 ug PHA)</u>	r	b	β	sr^2
Step One: BDI	*-.28	-3.44	-.28	*.08
Step Two: Intensity of Life Events	*-.36	-.42	*-.31	*.10

Table 32C.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 2.50 ug PHA-Stimulated Lymphocyte Proliferation Prior to a Midterm Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(2.50 ug PHA)</u>	r	b	β	sr^2
Step One: BDI	-.27	-3.91	-.27	.07
Step Two: Intensity of Life Events	-.08	-.05	-.03	.00

* $p < .05$

Table 33A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Emotional Containment plus Passivity on Percentage Change of 0.625 ug PHA-Stimulated Lymphocyte Proliferation Prior to a Midterm Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(0.625 ug PHA)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	-.27	-5.08	*-.29	*.08
Step Two: Emotional Containment plus Passivity	-.14	*-5.75	*-0.58	*.18

Table 33B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI) Scores & Intensity of Major Life Events on Percentage Change of 1.25 ug PHA-Stimulated Lymphocyte Proliferation Prior to a Midterm Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(1.25 ug PHA)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	.12	1.03	.12	.02
Step Two: Emotional Containment plus Passivity	-.24	-3.00	*-.67	*.21

Table 33C.

Hierarchical Regression Analysis of the Effects of Beck Depression Inventory (BDI) Scores & Use of Emotional Containment plus Passivity Coping on Percentage Change of 2.50 ug PHA-Stimulated Lymphocyte Proliferation Prior to a Midterm Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(2.50 ug PHA)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	.07	.44	.07	.00
Step Two: Emotional Containment plus Passivity	*-.40	-3.21	*-.85	*.38

* $p < .05$

Table 34A.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Mastery & Life Satisfaction Scores on Percentage Change of 1.0 ug Con A-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Final Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(1.0 ug Con A)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	.17	3.60	.17	.03
Step Two: Mastery	*.41	*8.93	*.46	*.14
Step Three: Life Satisfaction	*.64	**59.06	**81	**34

Table 34B.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Mastery & Life Satisfaction Scores on Percentage Change of 2.0 ug Con A-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Final Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(2.0 ug Con A)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	-.28	-5.74	-.28	.08
Step Two: Mastery	**59	11.65	**63	**27
Step Three: Life Satisfaction	*61	31.54	*54	*16

Table 34C.

Hierarchical Regression Analysis for the Effects of Beck Depression Inventory (BDI), Mastery & Life Satisfaction Scores on Percentage Change of 5.0 ug Con A-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Final Examination.

<u>Criterion Measure:</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u> <u>(5.0 ug Con A)</u>	<u>r</u>	<u>b</u>	<u>β</u>	<u>sr^2</u>
Step One: BDI	-.12	-1.96	-.12	.02
Step Two: Mastery	**54	10.09	**69	**32
Step Three: Life Satisfaction	*58	35.30	*64	*24

* $p < .05$ ** $p < 0.01$

Table 35.

Simple Regression Analyses for the Effect of Mastery on Percentage Changes of 0.625, 1.25 & 2.50 ug PHA-Stimulated Lymphocyte Proliferation 24 Hours Prior to a Final Examination.

<u>Criterion Measures</u> <u>% Change of</u> <u>Lymphocyte Proliferation</u>	<u>r</u>	<u>r²</u>	<u>β</u>	<u>F</u>
<u>Dose:</u> .625 ug PHA	*.41	*.168	*.41	*4.44
<u>Dose:</u> 1.25 ug PHA	** .61	** .372	** .61	**12.72
<u>Dose:</u> 2.50 ug PHA	** .63	** .396	** .63	**13.63

* p < .05   ** p < 0.01

Table 36.

Demographic Information (+SEM) for Control, Typical Major Depressive, Atypical Major Depressive, Typical Dysthymic & Atypical Dysthymic Subjects Participating in Experiment 4.

Group	Total N	Gender	Age (yrs.)
Control	17	8 Male, 9 Female	37.3 (2.37)
Typical MDD	10	5 Male, 5 Female	42.9 (3.91)
Atypical MDD	16	3 Male, 16 Female	40.8 (2.42)
Typical Dysthymic	32	18 Male, 14 Female	43.2 (1.97)
Atypical Dysthymic	31	12 Male, 19 Female	38.7 (1.72)

Table 37.

Baseline Clinical Efficacy Measures (+SEM) for SSRI & Placebo Subjects in All Depressive Subgroups in Experiment 4.

Group	HAM-D	HAM-A	MADRS	CGI
Typical MDD				
SSRI	26.60 (1.69)	Not Meas.	26.90 (4.69)	Not Meas.
Placebo	20.00 (0.00)	Not Meas.	Not Meas.	Not Meas.
Atypical MDD				
SSRI	22.78 (1.51)	Not Meas.	27.75 (5.56)	Not Meas.
Placebo	21.66 (0.88)	Not Meas.	Not Meas.	Not Meas.
Typical Dysthymic				
SSRI	18.30 (0.85)	16.84 (1.42)	24.23 (0.79)	4.33 (0.33)
Placebo	17.40 (0.94)	13.82 (1.49)	22.00 (1.79)	3.75 (0.25)
Atypical Dysthymic				
SSRI	17.00 (0.54)	14.61 (1.97)	23.92 (1.04)	4.00 (0.00)
Placebo	17.54 (0.81)	15.64 (1.21)	24.54 (1.11)	4.00 (0.00)

Table 38.

Mean HAM-D & MADRS (+SEM) Scores for Typical & Atypical Dysthymic Subjects Following 12 Weeks of Treatment.

Group	HAM-D		MADRS	
	Baseline	Week 12	Baseline	Week 12
Typical Dysthymic				
SSRI	18.30 (0.85)	4.83 (1.20)	24.23 (0.79)	7.25 (1.71)
Placebo	17.40 (0.94)	10.50 (3.98)	22.00 (1.79)	13.42 (3.69)
Atypical Dysthymic				
SSRI	17.00 (0.54)	5.18 (1.74)	23.92 (1.04)	9.45 (2.66)
Placebo	17.54 (0.81)	9.17 (2.38)	24.54 (1.11)	16.00 (2.28)

Figure 1. Mean (+SEM) basal peak PMA-stimulated neutrophil activity (r.l.u.) as a function of Gender and Beck Depression Inventory (BDI) classification (Low, Moderate or High).

Figure 2. Mean (+SEM) concentrations of plasma ACTH (pg/ml), cortisol (ug/dl), and prolactin (ug/L) as a function of a simple laboratory challenge (control, arithmetic challenge or a clinical interview) over time (min.).

Figure 3. Mean (+SEM) plasma norepinephrine (NE) and plasma epinephrine (Epi) concentrations (pg/ml) as a function of a simple laboratory challenge (control, arithmetic challenge or clinical interview) over time (min.).

Figure 4. Mean (+SEM) Con A- (1, 2 and 5 ug) and PHA- (.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation as a function of a simple laboratory challenge (control, arithmetic challenge or clinical interview) over time (min.).

Figure 5. Mean (+SEM) concentrations of plasma ACTH (pg/ml) and cortisol (ug/dl) as a function of Beck Depression Inventory (BDI) classification (Low or High) and a complex laboratory stressor over time (min.).

Figure 6. Mean (+SEM) plasma norepinephrine (NE) and plasma epinephrine (Epi) concentrations (pg/ml) as a function of Beck Depression Inventory (BDI) classification (Low or High) and a complex laboratory challenge over time (min.).

Figure 7. Mean (+SEM) Con A- (1, 2 and 5 ug) and PHA- (.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation as a function of a complex laboratory challenge over time (min.).

Figure 8. Mean (+SEM) concentrations of plasma ACTH (pg/ml), cortisol (ug/dl), and prolactin (ug/L) at baseline and at 30-60 min. prior to an Introductory Psychology examination.

Figure 9. Mean (+SEM) percent change of concentrations of plasma prolactin (ug/L) 30-60 min. prior to an Introductory Psychology examination as a function of Beck Depression Inventory (BDI) classification (Low, Moderate or High).

Figure 10. Mean (+SEM) concentrations of norepinephrine and epinephrine (pg/ml) at baseline and 30-60 min. prior to an Introductory Psychology examination.

Figure 11. Mean (+SEM) Con A-(1, 2 and 5 ug) and PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation at baseline and 30-60 min. prior to an Introductory Psychology examination.

Figure 12. Mean (+SEM) concentrations of plasma ACTH (pg/ml), cortisol (ug/dl), and prolactin (ug/L) among subjects tested at baseline and 24 hours prior to a midterm examination session.

Figure 13. Mean (+SEM) concentrations of plasma cortisol (ug/dl) among subjects tested at baseline and 24 hours prior to a midterm examination session, as a function of Beck Depression Inventory (BDI) classification.

Figure 14. Mean (+SEM) concentrations of plasma ACTH (pg/ml), cortisol (ug/dl), and prolactin (ug/L) among subjects tested at baseline and 24 hours prior to a final examination session.

Figure 15. Mean (+SEM) Con A-(1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation 24 hours prior to a midterm exam.

Figure 16. Mean (+SEM) Con A-(1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation 24 hours prior to a final exam.

Figure 17. Mean (+SEM) Con A- (1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation 24 hours prior to a final exam and 10-14 days after cessation of the final exam period (n = 10).

Figure 18. Mean (+SEM) peak PMA-stimulated macrophage & neutrophil activity at baseline & 24 hours prior to a midterm exam period.

Figure 19. Mean (+SEM) peak PMA-stimulated macrophage & neutrophil activity at baseline & 24 hours prior to a final exam period.

Figure 20. Mean (+SEM) peak PMA-stimulated macrophage & neutrophil activity at baseline & 24 hours prior to, and 10-14 days after the cessation of a final exam period.

Figure 21. Mean (+SEM) Con A-(1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation at baseline among control, typical major depressive, atypical major depressive, typical dysthymic, and atypical dysthymic subjects.

Figure 22. Mean (+SEM) Con A-(1, 2 and 5 ug) & PHA-(.625, 1.25 and 2.5 ug) stimulated lymphocyte proliferation at baseline & following 12 weeks of SSRI treatment among dysthymic subjects.

Dysthymic Subjects

Figure 23. Mean (+SEM) Con A-(1, 2 and 5 ug) stimulated lymphocyte proliferation at baseline & week 12 among dysthymic subjects responding to SSRI treatment.

Dysthymic Responders

Appendix A

INFORMED CONSENT

EFFECTS OF LIFE EVENTS AND ADVERSE ENVIRONMENT ON NEUROENDOCRINE, NEUROCHEMICAL AND IMMUNE FUNCTIONS

I _____ consent to participate in a study for which Dr. A.V. Ravindran and Dr. H. Anisman are the principle investigators.

In general, the purpose of the study is to determine whether the stressors you have experienced are related in any way to several chemicals in your blood. By measuring biological chemicals in the blood and relating these measures to mood states, information might be obtained which may assist clinicians in diagnosing and treating various illnesses.

Blood samples will be taken on three separate occasions: at the beginning of the study, the afternoon prior to your first examination and then 24 hours after your first examination. Each visit will take approximately 5 minutes each. On each occasion, approximately 25 ml of blood (approximately 3-4 small sampling tubes identical to those at a doctor's office) will be taken over a 2 minute period.

During the first visit, you will be asked to complete several questionnaires regarding your mood and the major and minor life stressors you have encountered.

Your participation in this study is completely voluntary and you may withdraw from it at any time without affecting your academic/clinical treatment. Your identity will be kept confidential at all times.

If any additional information regarding this study is desired, you may contact Dr. Anisman (520-2600 ext. 2699) or Dr. Ravindran (722-6521 ext. 6943). Additionally, if you have any ethical concerns about this study, you may contact Dr. Lise Paquet at 520-2600 ext. 2692.

_____
Date

_____
Name of Participant

_____
Signature of Participant

_____
Date

_____
Name of Investigator

_____
Signature of Investigator

INFORMED CONSENT

EFFECTS OF LIFE EVENTS AND ADVERSE ENVIRONMENT ON NEUROENDOCRINE, NEUROCHEMICAL AND IMMUNE FUNCTIONS

I, _____ consent to participate in a study for which Dr. A.V. Ravindran and Dr. H. Anisman are the principle investigators.

In general, the purpose of the study is to determine whether the stressors you have experienced are related in any way to several chemicals in your blood. By measuring biological chemicals in the blood and relating these measures to mood states, information might be obtained which may assist clinicians in diagnosing and treating various illnesses.

Blood samples will be taken on two separate occasions: at the beginning of the study and again just prior to your final academic examination. On the first occasion, a volume of 130 ml of blood will be taken (less than 1/4 of the amount given by Red Cross donors) over a 1.5 hour period, while on the second occasion 20 ml of blood will be taken over a 2 minute period.

During the first visit you will be asked to complete several questionnaires regarding your mood and the major and minor stressors you have encountered. Additionally, during the first visit you will receive a challenge consisting of a delivery of a 5 minute speech followed by a series of arithmetic problems. During the speech portion, you will be asked to speak about either a neutral topic, or an emotionally charged topic of a personal nature. Your performance in these situations will be monitored by a videocamera. As well, during these times, your blood will automatically be taken to assess the effects of the challenge on your blood chemistry.

Your participation in this study is entirely voluntary and you may withdraw at any time without affecting your current or future academic/clinical treatment. Your identity will be kept completely confidential at all times.

If any additional information regarding this study is desired, you may contact Dr. Anisman (788-2600 ext. 2699) or Dr. Ravindran (722-6521 ext. 6943). Additionally, if you have any ethical concerns about this study, you may contact Dr. Lise Paquet at 788-2600 ext. 2692.

_____
Date

_____
Name of Participant

_____
Signature of Participant

_____
Date

_____
Name of Investigator

_____
Signature of Investigator

INFORMED CONSENT

EFFECTS OF LIFE EVENTS AND ADVERSE ENVIRONMENT ON NEUROENDOCRINE, NEUROCHEMICAL AND IMMUNE FUNCTIONS

I, _____ consent to participate in a study for which Dr. A.V. Ravindran and Dr. H. Anisman are the principal investigators.

In general, the purpose of the study is to determine whether the stressors you have experienced are related in any way to several chemicals in your blood. By measuring biological chemicals in the blood and relating these measures to mood states, information might be obtained which may assist clinicians in diagnosing and treating various illnesses.

Blood samples will be taken on two separate occasions: At the beginning of the study and again just prior to your final academic examination. On these occasions, a volume of about 130 ml of blood will be taken (less than 1/4 of the amount given by Red Cross donors). The first samples will be taken over a 1.5 hr period, while the latter sample will be taken over approximately 2 min. In addition to collecting blood, saliva may be collected from you so that chemicals in saliva can be measured. This entails placing a "salivette" (a small cotton filled container) in your mouth for several minutes.

At the first visit you will be asked to complete several questionnaires regarding your mood and the major and minor stressors you have encountered. Additionally, during the first visit you will receive a challenge consisting of either a series of arithmetic problems, a maze solving task, or an interview regarding stresses you have encountered. Your performance in these situations will be monitored by a videocamera.

As well, during these times blood will automatically be taken to assess the effects of the challenge on your blood chemistry.

Your participation in this study is entirely voluntary and you may withdraw at any time without affecting your current or future academic/clinical treatment. Your identity will be kept completely confidential at all times.

If additional information regarding this study is desired, you may contact Dr. Anisman (788-2600 #2699) or Dr Ravindran (722-6521 #6943). Additionally, if you have any ethical concerns about this study, you may contact Dr. Lise Paquet at 788-2600 #2692.

Date	Name of Participant	Signature of Participant
Date	Name of Investigator	Signature of Investigator

SUBJECT INFORMATION

Init's: ____ Age: ____ Study # ____ I.D. # ____

Date: ____/____/____ Male/Female ____ Date of Birth: ____/____/____
Y M D Y M D

Educational Level: (Indicate highest level achieved)

Less than 7 years: _____1

Jr. High School: _____2

Partial High School: _____3

High School Graduate: _____4

Partial Univ./College: _____5

Univ./College Graduate: _____6

Postgrad./Professional School: _____7

Years in University ____ (yrs) Full-time: Yes ____ No ____

Presently Employed: Yes ____ No ____ Occupation: _____

Marital Status: Single ____1 Method of Income: Working ____1

Married ____2 Pension ____2

Sep/Div ____3 UIC ____3

Widowed ____4 Welfare ____4

# of Children: _____ None ____5

Accomodation: Alone _____1

Family Home (Spouse) _____2

Family Home (Parents) _____3

Friend/Roommate _____4

Halfway/Boarding Home _____5

Shelter _____6

BRIEF MEDICAL HISTORY

I.D. # _____

1. Are you currently taking any type medication? Yes___1 No___0

If YES, specify: _____

2. Family History: Specify type of illness & family relationship.

	<u>TYPE</u>	<u>WHO IN FAMILY</u>
Physical Illness	_____	_____
Psychiatric Illness	_____	_____
Substance Abuse	_____	_____
Other	_____	_____

3. Do you smoke? Yes___1 No___0

If yes: # Cigarette/day___ # Cigars/day___ #Pipes/day___

4. Do you drink alcohol? Yes___1 No___0

If yes: Beer___ Wine___ Liquor___

5. How much alcohol do you consume during the week?

No drinks/week	___0
Less than 1-2 drinks/week	___1
1-2 drinks per week	___2
1-2 drinks/day, at least 4 days/week	___3
More than 3 drinks/day, at least 4 days/week	___4

6. Do you use any abusable substances? Yes___1 No___2
(e.g. marijuana)

If yes: Specify type & frequency_____

7. Have you ever had a head injury? Yes___1 No___2

NOTE TO USERS

Copyrighted materials in this document have not been filmed at the request of the author. They are available for consultation at the author's university library.

**Appendix A
Beck Inventory
Perceived Stress Scale
Life Events Scale
The Hassles Scale
The Uplifts Scale
Coping Strategies Scale
Revised UCLA Loneliness Scale
Quality of Life Questionnaire**

UMI

Appendix B

#4.

PLEASE CIRCLE THE APPROPRIATE ANSWER:

1. How have you been doing in this particular course? (Circle one only)

A+	A	A-
B+	B	B-
C+	C	C-
D+	D	D- F

2. Being as realistic as possible, how do you think you will do in this course? (Circle one)

A+	A	A-
B+	B	B-
C+	C	C-
D+	D	D- F

3. What were your initial expectancies? (i.e. how did you think you would do?)

A+	A	A-
B+	B	B-
C+	C	C-
D+	D	D- F

4. What final mark will you be satisfied with?

A+	A	A-
B+	B	B-
C+	C	C-
D+	D	D- F

5. How much does this exam stress you?

1.....2.....3.....4.....5.....6.....7
not at all   average   extremely

6. Have you been sick (cold, flu, etc.) in the past 2 weeks? (Circle)   YES   NO

OVER →

7. Which examination are you taking? _____

PERCEIVED STRESS SCALE

I.D. # _____

The questions on this scale ask you about your feelings and thoughts DURING THE LAST MONTH. In each case, you will be asked to indicate how OFTEN you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each question fairly quickly. That is, don't try to count up the number of times that you felt a particular way, but rather indicate the alternative that seems like a reasonable estimate.

For each question choose from the following alternatives:

0=NEVER   1=ALMOST NEVER   2=SOMETIMES   3=FAIRLY OFTEN   4=VERY OFTEN

- ____ 1. How often have you been upset because of something that happened unexpectedly?
- ____ 2. How often have you felt that you were unable to control the important things in your life?
- ____ 3. How often have you felt nervous and "stressed"?
- ____ 4. How often have you dealt successfully with irritating life hassles?
- ____ 5. How often have you felt that you were effectively coping with important changes that were occurring in your life?
- ____ 6. How often have you felt confident about your ability to handle personal problems?
- ____ 7. How often have you felt that things were going your way?
- ____ 8. How often have you found that you could not cope with all the things that you had to do?
- ____ 9. How often have you been able to control irritations in your life?
- ____ 10. How often have you felt that you were on top of things?
- ____ 11. How often have you been angered because of things that happened that were outside of your control?
- ____ 12. How often have you found yourself thinking about things that you have to accomplish?
- ____ 13. How often have you been able to control the way you spend your time?
- ____ 14. How often have you felt difficulties were piling up so high that you could not overcome them?

Appendix C

MASTERY

I.D.# _____
DATE _____

Using the scale provided as a guide, indicate How strongly you agree or disagree with each of the following statements by Writing the corresponding number beside the question. Give only one answer for each statement.

Strongly Disagree	Moderately Disagree	Neither Disagree nor Agree	Moderately Agree	Strongly Agree
1	2	3	4	5

---

1. There is really no way I can solve some of the problems I have. _____

2. Sometimes I feel that I'm being pushed around in life. _____

3. I have little control over the things that happen to me. _____

4. I can do just about anything I really set my mind to. _____

5. I often feel helpless in dealing with the problems of life. _____

6. What happens to me in the future mostly depends on me. _____

7. There is little I can do to change many of the important things in my life. _____