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The Psychological Modulation of the Immune System: A Meta-Analysis

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THE PSYCHOLOGICAL MODULATION OF THE IMMUNE SYSTEM:

A META-ANALYSIS

BY

SARA D. COTTRILL

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE

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Abstract

In the mid seventies, Robert Ader and Nicholas Cohen (1975) conducted and published a series of experiments that are generally recognized as a major turning point for the behavioral and physical sciences. In classical conditioning experiments, Ader and Cohen were able to weaken the immune system reaction against foreign material in rats. The experiments demonstrated that the "self-regulating and autonomous" immune system was vulnerable to behavioral factors. These experiments seemed to galvanize a community of scientists who had hypothesized like scientists and philosophers before them the role of emotional states in influencing physiological processes.

The preeminent discipline which has evolved in this dynamic field of study is psychoneuroimmunology. Being an interdisciplinary field, it has begun to study extensively the role of psychological and behavioral factors in physiological processes, namely the immune and endocrine systems. The implications of this research could have a profound impact on the major, complex diseases which plague the health profession. Since the mid seventies, a plethora of research focused on the relationship between psychological/behavioral events and the immune system. Although there have been many narrative reviews of the literature, there have been only a few meta-analyses performed.

The objective of this investigation was to procure all research that focused on the psychological modulation of the immune system in humans and to measure the magnitude of effect of the psychological factors in each study. In addition, 7 unique characteristics (predictors) of the studies included in the meta-analysis were analyzed to determine if they covaried significantly

with study outcomes. These results would shed light on the analytical questions of explanation and prediction.

For the meta-analysis, 75 statistical tests were transformed into common metrics: Z scores and one-tailed probability levels for the significance level and product-moment correlation's, Fisher's Zs and Cohen's d for effect size. The results of the analysis indicated small to large effect sizes for individual statistical tests. When tests were grouped according to type of immunologic measure (innate, humoral or cellular immunity), slightly stronger results were obtained.

The 7 characteristics were publication date, type of population, validity, experiment situation, type of treatment, and direction of modulation. The results of the analyses indicated that the characteristics or predictors covaried significantly with study outcomes.

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CHAPTER I

Introduction

Statement of Problem

Voodoo Death. Shamanism. Fire-Walking. These are extraordinary phenomena that evoke skepticism and disbelief in most and categorical denial in others. However, for a small minority these phenomena seduce the inquisitive nature of the intellect. They beckon the thoughts of individuals from the dogma of natural science to the experience of transcendentalism. These events for a small minority epitomize the constant, but sometimes impetuous, harmony between mind and body, the endless celebratory interplay between psychic energy and somatic functions. Voodoo death, shamanism, and fire-walking are real life representations of the issues that are grist for the mill for the age-old mind/body quandary: Are mind and matter two different things or the same thing viewed from two different perspectives? Is consciousness an epiphenomenon? Or is consciousness an isomorphic phenomenal counterpart of underlying brain activity?

The import of consciousness is elusive in the western culture. It is elusive not merely in the philosophical literature where it has been intellectualized for centuries, but elusive on the societal level where the individual defines the fundamental nature of life. This is evident when one looks to the two major societal forces in the western culture, religion and science. Religion and science are arguably the most influential bodies of thought that the individual encounters. Permeating through every facet of the modern cultures, religion and science shape the answers to the existential questions that an individual asks. Yet, the realities they construct are different from one another. Epitomizing

these differences is consciousness. From the religious perspective, it is a supremely powerful force, an autonomous energy (Hayes, 1988). From the scientific community's perspective, it is a construct which does not have any physical attributes. Hence, it is a meaningless referent (Tageson, 1982).

However, the import of consciousness, albeit elusive presently, is becoming of great interest as our understanding of the human physiological processes grows. During the past few decades, there has been a expansive amount of research in various scientific disciplines which has not only intensified the complexity of physiological processes but also the dynamic aspect. The result of this has made many scientists start to reconceptualize the interrelationship between the nervous, endocrine, and immune systems, and the relationship between mind and body.

Scientific discoveries such as peptides in the immune and endocrine systems (Pert et al, 1985), hormones interacting with the immune system and the immune system interacting with brain (Felton & Felton, 1991) underscore and heighten the complexity of physiological functioning. Yet, it is the scientific discoveries that include the psychophysiological factors that highlight the dynamic aspects. These scientific discoveries are having a profound impact. And although there are many implications, one of the most important of this seminal work is that it allows us to look at disease in a different way. This different way may provide greater insight into the complex diseases that confronts us.

Metabolic, infectious, neoplastic, autoimmune, genetic and nutritional are the six major categories of disease. During this century, there has been considerable success in dealing with two types of disease: infectious and nutritional (Feuerstein, Labbe & Kuczmierczyk, 1986). For example, the mortality rate for tuberculosis and influenza/pneumonia has decreased; it was 25% in 1900 and in 1980 the rate was only 5% (National Center for Health Statistics, 1985). However, progress for other diseases has not been as successful. Cancer and cardiovascular disease comprised approximately 70% of the mortality rate in 1980. This has increased since 1900 when it was only 20% (National Center for Health Statistics, 1985). These statistics depict a basic issue confronting the health profession: multifactorial diseases in which psychological/behavioral factors play a role are problematic and complex. The role of psychological/behavioral factors in disease has only recently come under investigation.

One field which has emerged and extensively investigated these factors is psychoneuroimmunology. Although there have been many narrative reviews of the literature, only a few meta-analyses have yet to be performed. Therefore, the objective of this investigation will be to procure research that focuses on the psychological modulation of the immune system in humans and to measure the magnitude of effect of the psychological factors in each study. The effects of different psychological factors will be compared and the relationship to the characteristics of the studies will be explored. The goal of the study will be to apply the results to the mind/body relationship.

Historical Perspective

It is conceivable that in years to come the last quarter of this century will be thought of as the beginning of the rebirth or renaissance of *consciousness*. The consciousness that is being talked about is not that which traditional psychology has studied: altered states (sleep, hypnotic, drug induced), levels of consciousness (unconscious, preconscious, conscious), aspects/processes of the mind, etc. Instead, it is the life force that Greek philosophers such as Thales (ca: 560 B.C.) professed. There have been numerous independent, but related developments in various scientific disciplines over the past few decades which are creating a new perspective on the mind/body relationship. The synthesis of these developments is leading to a new era of intellectual thought, one in which a metaphysical model could play a greater role along side a mechanistic paradigm/theory.

The developments by themselves or paired with a few others may not accurately portray the transformation or evolution of scientific thought. However, when one reviews all of the events in various scientific domains related to somatic functions, one observes a trend away from a pure mechanistic model to a more progressive model in which there is an interconnectedness between mind and body.

The developments comprise a wide range of scientific activity, including the formation of new disciplines, major theoretical shifts, the integration of several disciplines to compose new interdisciplinary fields and a plethora of research activity that is fortifying the mind/body relationship.

From one perspective, these developments are all but antithetical to the direction that those most involved with somatic function, namely medicine, have taken. Closely aligned with mechanistic or reductionistic principles since the Renaissance, medicine has been exclusively devoted to describing basic processes in physiochemical terms. It has focused on the micro and macro physical structures of the body, their relationships to one another and their proper functioning.

Franz Alexander (1939) articulated the organizing principle for the medical profession in his paper entitled, "Psychological Aspects of Medicine." He stated: "The fundamental philosophical postulate of modern medicine is that the body and its function can be understood in terms of physical chemistry, that living organisms are physio-chemical machines and the ideal of the physician is to become an engineer of the body" (p. 3). The individual is conceptualized and defined only in terms of a conglomeration of mechanistic components. Only those things which have a physical attribute are considered to play a role in the federation of the body.

The accomplishments of modern medicine reflect this philosophical position. Starting in the 17th century with anatomical and physiological investigations that produced fairly precise structural make-up of man to genetic engineering, growth factors, and hormonal therapy in the 20th, medicine has arduously adhered to understanding and defining the individual in materialistic terms. This position, which has excluded factors that are not mechanistic in nature, has served as an outline of policy and conduct for medicine.

The new direction being undertaken boldly goes beyond these mechanistic boundaries. The common denominator in all these developments except one is that consciousness plays a meaningful role in physiological function. These developments are defining a new era.

The first major development was the emergence of a new area, modern scientific medical psychology, more commonly known as psychosomatic medicine. When it first came into existence in the 1930's, psychosomatic medicine or psychosomatics was an area devoted to studying the role of emotion in its relationship to disease (Lipowski, 1985). The scientific discipline recognized the individual as an interactive organism and not just a collection of organs. The recognition of psychological factors, psychologism, as a causative role in disease was a bold one for the time. Psychologism was thought to be more appropriately aligned with medical art than the staunch medical scientific tradition (Alexander, 1939).

Alexander (1939) explains that when medicine became the youngest member of the natural science family during the 19th century, its mode of operating was patterned after or based on physics, chemistry, anatomy, and physiology. This was reinforced by the work in modern bacteriology, surgery, pharmacology, and chemotherapy. In addition, Pasteur and Koch's work in pathogenic micro-organisms in infectious disease and the discovery of external factors such as dust particles influencing tissue changes only seem to substantiate the medical community's position.

Less than a decade later during the 1940's, articles which focused on the investigation of physiological and psychological aspects of behavior were appearing in various psychological journals. Although books and articles pertaining to this area had appeared sporadically over the past century, these articles marked the embryonic beginning of a new subdiscipline in psychology, psychophysiology (Ax, 1964). It wasn't until the early 1960's that this area solidified, forming its own journal. The principle tenet of this academic group: the science which concerns those physiological activities which underlie or relate to psychic function (Ax, 1964).

As psychophysiology was defining its mission in the early 1960's and its research was evolving into a more cohesive body of scholarly work, George Solomon and Rudolf Moos (1964) published a paper that investigated the relationship between the immune system, emotion, and disease. The major theoretical statement of the paper was that "...auto immunity may be related to relative immunological incompetence and that such immunological incompetence in turn might be related to emotional stress and both anxious and depressive affect, which are associated with elevation of adrenal cortical steroid hormones" (p.658). Their pioneering work is considered one of the first studies in a field which came to prominence some 20 years later (Boindi & Kotzalidis, 1990). That field is psychoneuroimmunology.

Psychoneuroimmunology is composed of diverse scientific areas whose focus is how the brain/mind affect health. Some of the areas which are represented in this new discipline are: psychology, neuroanatomy, neuroendocrinology, oncology, and immunology. However, although Solomon

and Moos are cited first for this revolutionary area in psychological research in this dynamic new field, their research was greatly enhanced by the work of Robert Ader and Nicholas Cohen (Dienstrey, 1991). In fact the research that these two scholars published served as a catalyst for this area of research. In a series of experiments that used standard classical conditioning paradigms, Ader and Cohen were able to weaken the immune system reaction against foreign material in rats. These experiments demonstrated that the "self-regulating and autonomous" immune system could be manipulated by external events. This opened the door to a plethora of research that focused on the relationship between mental phenomena and immunosuppression.

Representing only some of the revolutionary research that was going on during the 1960's and 70's, these scientific investigations were some of the landmarks for the change in philosophy. Some of the most significant philosophical developments occurred in the field of psychology. Roger Sperry began writing about the "emergent properties" of the brain in the mid to late sixties. Sperry(1969) wrote about the relationship between mind/consciousness and brain activity and the directive role that consciousness has in regard to the flow of cerebral excitation.

In the early to mid seventies perhaps the most significant development was the mentalist/cognitive/consciousness revolution. The revolution created a dramatic shift in the behavioral sciences. This resulted in the acceptance of consciousness and the subjective experience in a new explanatory framework (Sperry, 1988). Prior to this turnabout, the relationship between the nature of the mind and brain

activity was not acknowledged or recognized by the scientific community. However, the advent of the cognitive/mentalistic/consciousness revolution changed this. As Roger Sperry (1988) states, "the full range of contents and qualities of inner experience...are not only given a new legitimacy in science, but also given primacy over the more basic physiochemical forces" (p.609).

Finally, in the late seventies and early eighties, a new perspective on health emerged. This perspective included a multifactorial approach to disease. The multifactorial approach proposed that behavioral factors in addition to biological and environmental play a major role in disease. As a result of this, the formation of a new subdiscipline and discipline evolved. They are health psychology and behavioral medicine. From one perspective, these two areas represent the culmination of scientific research and philosophy over the last several decades by looking beyond the mere physical components of disease.

Behavioral medicine and health psychology along with all the other scientific developments which have been reviewed briefly attest to the breadth of a new scientific perspective. And tantamount to the breadth of these scientific developments is the depth of the research in the individual disciplines and subdisciplines. It is the depth of these discoveries that fortifies the "interconnectedness" aspects of this new perspective in science. While the complex relationship between psychological activities and physiological events are being recognized, the implications are really just beginning to be realized.

The research investigations on stress serves as an excellent example of this. Stress is the "nonspecific response of the body to any demand made upon it" (Selye, 1979). Psychophysiologicals, endocrinologists and other scientists have been investigating this phenomenon since the beginning of the century (Johnson & Anderson, 1990). As a result of decades of investigations, researchers have documented 1400 physiological changes related to the stress response (Johnson & Anderson, 1990). Some of the cited physiological changes are alterations in levels of vasopressin, prolactin, growth hormone, ACTH, luteinizing hormone, thyrotropin, adrenaline, and noradrenaline (Johnson & Anderson, 1990).

Parenthetically, as the number of physiological changes has grown, the number of physiological systems involved has also changed. As Johnson & Anderson (1990) report, Walter Cannon, a preeminent physiologist, conceptualized that the stress response entailed the sympathetic nervous system giving rise to a massive sympathetic activation to trigger a fight or flight response. Currently, as these authors report, the neocortex, limbic system and hypothalamus are affected by a stressor. This group then influences the autonomic system and multiple neuroendocrine responses (Johnson & Anderson, 1990). Although the reverberating effects of stress are fascinating in themselves, the implications of it are even more interesting.

One profound implication is the potential of modulating the immune system when levels of certain hormones are altered by stress (Levy, 1991). Shavit (1991) reports scientific work that supports the role of stress in modifying the immune responses by changing the levels of

hormones, neurotransmitters, and neuropeptides. Prolactin (Bernton et al., 1991), growth hormones (Kelley, 1991), and catecholamines (Roszman & Carlson, 1991) have been also cited as playing a role in immune regulation. If the immune response is impeded or impaired, then the body is at risk for not only infectious diseases but also neoplastic diseases (Levy, 1991). It is because of this complex relationship between psychological activities and physiological events that Sandra Levy (1991) cites behavior as a "relevant biological response modifier" (p.124). She would go on to define behavior in the "broadest sense" which includes thoughts and emotions.

The breadth and depth of the scientific research pertaining to the influence of psychological activities on physiological events is abundant. It is forging a new perspective. However, the development which will solidify this new perspective and bring it to the forefront of science may be modern physics (Pert, 1993). The events going on in modern physics could be the most significant development of all. Although there is great resistance to apply that of subatomic physics to the mind/body issues, modern physics has changed the way matter is perceived. Mass is seen as a form of energy and not an indestructible material substance (Capra, 1982). Along with changing the composition of mass from substance to energy and other concepts mentioned, previously, the world and its contents is no longer perceived as static, but as a dynamic interconnected field of energy. Given that physics is the study of matter and energy, the advancements of modern physics could have profound implications for medicine. It could provide valuable insights into the nature of some challenging diseases.

Immune System

At any given moment there is an infinite amount of foreign material - living and non living - that confronts and assaults the human body on a constant basis (Nossal, 1992). Having the ability to cause serious illness, they pose a threat to the body. Without being consciously aware of it, our body's defense mechanisms are relentlessly seeking out and destroying these microscopic foes. The microscopic foes are called antigens and immunogens and they stimulate a specific group of defense mechanisms which are collectively called the immune system. It is the awesome responsibility of the immune system to protect the body against foreign invaders that can cause disease. This includes the special ability of defense mechanisms being able to differentiate between foreign molecules and the molecules that compose the body. In the literature, this is called self-nonsel self recognition.

The immune system is one of three major physiological systems which have the ability to regulate certain functional processes or activities in the body. Like the endocrine and nervous systems, the immune system is extremely sophisticated and complex. Lymphocytes, for instance, have the ability to recognize and interact with almost any molecule that exists in nature. The number of antigen receptors that existing lymphocytes is proposed to be approximately 100,000,000 (Smith, 1992). Given the complexity of the immune system, an outline will be given for the purposes of this dissertation.

The immune system is broken down into distinct parts: innate immunity and acquired immunity. Innate immunity is defined as "...all those elements with which an individual is born and that are always

present and available on short notice to protect the individual from callings by foreign material"(Benjamini & Leskowitz, 1988, p.10).

Acquired immunity is defined as "... a consequence of an encounter with a foreign substance... develops only after to or immunization with a given substance. It develops against that substance which was used for immunization"(Benjamini & Leskowitz, 1988, p.12). The most salient factor when distinguishing these two centers around the *modus operandi* of these defense mechanisms. The defense mechanisms of acquired immunity are stimulated only when a prior contact with a foreign invader has existed. Given this prerequisite, the actions of acquired immunity are classified as "specific" as part of the profile for this type of immunity. The defense mechanism of innate immunity can be stimulated by a foreign invader regardless of prior contact. Hence, the action of innate immunity is classified as nonspecific (Benjamini & Leskowitz, 1988).

Innate immunity is made up of a number of operatives. Beginning with the skin and linings of the respiratory and gastrointestinal tract secreting various biochemical agents, these protective barriers offer the first line of defense against foreign substances. If a foreign substance passes these barriers, the next line of defense is various protein or protein-based substances which interfere in some way with the critical activities of a foreign substance. Interferons, for example, are produced when a foreign substance enters the body. They have the ability to stop the replication of numerous viruses. Another protein which is secreted is transferrin. This protein unites with molecules of iron. Since iron is a critical element for bacteria to survive, trans-

ferrin has a devastating impact on a microbe. Assisting in similar ways, many biochemical agents exist as part of innate immunity (Nossal, 1992).

The major component of acquired immunity is lymphocytes. Two types of lymphocytes exist: T lymphocytes (or T cells) and B lymphocytes (or B cells). Although these T and B cells come from stem cells in bone marrow, the maturation process occurs in two different places in the body for these different cells. T cells differentiate in the thymus and B cells in the bone marrow. These T and B cells go on to operate in different ways.

B cells secrete antibodies. Consequently, B cells do not interact directly with foreign substances. Instead, secreted antibodies from B cells move through the body's fluids such as blood, lymph or bile (Smith, 1992). B cells are identified with humoral immunity. Although the antibodies differ in terms of structure and function, the basic mission of antibodies is to negate harmful toxins, to encapsulate bacteria or to block receptor sites for the viruses. These antibodies are known as immunoglobulins (Ig). There are five main classes of Ig: IgG, IgM, IgA, IgD, and IgE (Nossal, 1992).

Whereas B cells do not interact directly with foreign invaders, T cells do. Since this is an exact action or the encounter is straightforward, this is classified as cellular immunity or cell-mediated immunity. The basic mission of the T cell is to destroy the foreign invader. T cells are broken down into two categories: helper and cytotoxic/suppressor T cells. The two categories of T cells are related to the two categories of antigens: histocompatibility complex class I and II antigens (Nossal, 1992).

Literature Review

The focus on and the study of the relationship between mind and body appears to be stronger with the passage of time. The shift in the behavioral sciences has resulted in a plethora of research in many scientific disciplines, which examine to various degrees the mind/body relationship: psychological modulation of the immune function, the interrelationship between immune, endocrine, and nervous system, elements of the neuroimmunological feedback loops, the interconnection among brain, psyche and immune mechanisms, etc. The research being done is not only elucidating the relationship between emotional and physical states, but it is also identifying underlying mechanisms which are playing a role in problematic diseases such as autoimmune and cancer (Batuman et al, 1990).

The actual number of journal articles and books published since the early 1980's substantiates the assertion that the mind/body relationship appears to be becoming stronger with the passage of time. In a literature search that specifically focused on the topic of psychoneuroimmunology, seven articles were published in psychology journals from 1983 to 1985. However, since 1987, over 65 articles have been published that dealt with the topic. The same pattern exists with other topic areas related to the mind/body relationship. For instance psychoimmunology was referenced in only 2 articles in the early 1980's and in 19 articles since 1987. In terms of books and chapters, there seems to be the same result. In 1987, only 3 books discussed the topic of psychoneuroimmunology and in 1991 there were 21 books.

Scientific research in laboratories with animals that explores conditioned alterations of the immune system typically use a Pavlovian or classical conditioning paradigm. The most basic elements of the paradigm are the unconditioned stimulus (UCS) and the unconditioned response (UCR). The UCS is an agent that elicits or produces a reaction from the organism. This unlearned reaction or response is the UCR. In a conditioning experiment, a neutral stimulus is paired sequentially or simultaneously with the UCS. At the time that the neutral agent is capable of eliciting a similar response to the UCR, the neutral agent becomes the conditioned stimulus (CS). The response that it evokes becomes the conditioned response (CR).

In an article which reviewed the most recent studies in the scientific purview of conditioned alterations of immunological activity, Robert Ader and Nicholas Cohen (1991) report on three major investigative areas. They are conditioned immunosuppression, conditioned immunoenhancement and conditioned compensatory responses. Conditioned immunosuppression is the ability to subdue an immunological response to an antagonist of the immune system via a previous neutral stimulus. Heightening or creating an immunological response via a previous neutral stimulus is called immunoenhancement. And a conditioned compensatory response is an immunological response which is achieved through classical conditioning, but is opposite of what is expected.

In this area of conditioned alterations of immunological reactivity, a common research protocol would use an immunosuppressor or immunoenhancer as the UCS. For instance, cyclophosphamide, frequently used, is an immunosuppressive drug that prevents or inhibits an immune

response. Cyclophosphamide (UCS) would be paired simultaneously with saccharin diluted water (CS). In order to measure the conditioned alteration, the rat/mouse would then be immunized with sheep red blood cells (SRBC). Researchers would measure the antibody response and then re-expose the animal to the CS. A second measure of the antibody response would be taken and compared to the first sample. If there is a conditioned immunomodulatory effect, there will be an attenuated anti-SRBC response.

Immunosuppression is the strongest area not only in terms of number of investigations, but also in terms of immunomodulatory effect. Results have been consistent when endeavoring to manipulate an immunological response. In addition to cyclophosphamide, previously mentioned, other immunosuppressive agents such as methotrexate have been used as an UCS. However, it is the research that has used cyclophosphamide as an immunosuppressive agent that yields the greatest amount of data. Using a number of dependent measures such as antibody responses to sheep red blood cells, lymphocytes proliferation, natural killer cell activity, white cells, etc., scientific research has demonstrated repeatedly the conditioned alteration of immunological reactivity.

As far as the research in the immunoenhancement domain, there have been many studies that have demonstrated the conditioned enhancement of the immune response. These studies like other studies in this area use the classical conditioning paradigm. However, the UCS is different. It is an agent that accelerates or promotes greater immunological activity instead of depressing it. Ader and Cohen report on various investigations that not only differ in terms of parameters, but also in

terms of validity. They present several investigations that demonstrate conditioned enhancement of the immune response, but are unable to be replicated. This may be due to the complicated nature of the immune system. However, Ader and Cohen survey several methodologically sound studies which demonstrate conditioned immunomodulatory effects. In these studies, a range of unconditioned stimuli which trigger an immune reaction were paired with a neutral stimulus. Levamisole, polyinosinic-polycytidylic acid (PolyI:C) and antigens which typically elicit immune responses serve as the unconditioned stimulus. All were successfully paired with a neutral stimulus. In one study which was reviewed by the authors, a discriminative stimulus paradigm was implemented. Results indicated that rat's immunological reactivity could be enhanced in this type of classical conditioning paradigm.

A conditioned compensatory response is an immunological response, as noted by Ader and Cohen, paradoxical in nature, i.e. a response that is in an opposite direction than what is expected. This area remains elusive because the only thing that is consistent is the response. This is an area which according to the authors "remains to be defined and elaborated"(p.623). There have been many models proposed that try to explain this enigmatic response. However, a definitive model has not been accepted, yet. Although the underlying mechanisms are unclear at the present time, this is a well established phenomenon.

There are other studies which use different classical conditioning paradigms to manipulate an immunological response. These studies usually use a physical event such as a foot shock as an UCS. Mormeade, Dantzer, Michaud, Kelley, and LeMoal (1988) conducted a study which examined the

effects of a stressful event (footshock) and what effect the ability to predict it would have on the immune system. In the experiment, it was demonstrated that the reactivity of splenocytes to concanalin A was decreased by a third when rats received inescapable footshock but increased by a third when footshocks were preceded by a warning signal. In another study (Dyck et al, 1990), a classical conditioning paradigm was used to determine if adrenal cortical secretion could be conditioned to environmental stimuli. The researchers paired recombinant interleukin-2 (IL-2) beta, which can stimulate the pituitary-axis to secrete corticosterone with environmental cues. The results indicate that adrenal cortical secretion can be conditioned to environmental stimuli. The treatment group's response was greater than the control group and another treatment group which was not re-exposed to the cues. In another study which identifies a potential underlying mechanism, Batuman, Sajewski, Ottenwellen, Pitman, and Natelson (1990) examined the effects of stress on T cells and tried to elucidate the underlying mechanisms in T cell suppression. The repeated exposure to stress resulted in a significantly lower number of T cells. Under further test conditions, it was shown that IL-2 was defective. Subsequently, this impaired immunoregulatory T cell generation, which is a predisposition to a malignancy or autoimmune disease.

The study of the psychological modulation of the immune system in human research is as vigorous as the animal research at the present time. The following studies are representative of research in the literature. They also demonstrate empirically the influence of emotional states on immunological function.

Kubitz, Peavy, and Moore (1986) examined the relationship of levels of salivary immunoglobulin A and health locus of control in 15 subjects with high stress and 15 subjects with low stress levels. The results indicated significant positive correlations for stress symptom scores and locus of control and significant negative correlation for immunological A and internality. The subjects with higher level of internal health locus of control seemed to have a particular vulnerability to stress. In another study (Green & Green 1987), 50 college students were randomly assigned to one of the following relaxation methods group: relaxation response, guided visualization, massage, lying quietly with eyes closed or a touching control group. Salivary immunoglobulin A (SIA) and salivary cortisol (SC) were measured before and after a 20 minute session. SIA increased in subjects in the relaxation response, guided visualization and massage groups. There were not any changes in SC levels.

Bloom and Smith (1987) examined two indicators of the immune system, natural killer cells and T cells, in 37 women who had experienced major life changes. Those who had experienced major life changes had lower natural killer cell activity than women with minor life changes. Assessment was completed in a psychiatric interview with several rating scales. The results also depicted a decrease in suppressor/cytotoxic cells and increase in the ratio helper T cells. Gruber, Hall, Hersh, and Dubois (1988) investigated the effects of relaxation and imagery on the immune responses in 10 people with metastatic cancer. After 7 months of relaxation and imagery training, the results of hormonal immunological assay which included interleukin-2 and

T cell mitogens in blood samples demonstrated that the immune cell function increased over the treatment period. Glaser (1986) assessed the plasma levels of 3 immunoglobulins (IgG, IgM, and IgA) in the blood samples of 40 medical students. Samples were taken 6 six weeks before examinations and on the day of examinations. The data showed increases in IgG, IgM, and IgA on the examination day. Although the data do not follow the typical trend of results, they do support the effect of a psychological state influencing the immune system.

Two prominent researchers in the area of the psychological modulation of the immune system are Janice Kiecolt-Glaser and Ronald Glaser. They have published numerous articles that focus on the interaction between psychological events and physiological function in the central nervous and immune systems. In addition to publishing many scientific investigations pertaining to the psychological modulation of the immune system, Kiecolt-Glaser and Glaser (1991) have also published a comprehensive review article on stress and the immune function in humans. Classifying psychological stressors into three categories: major stressful life changes (bereavement and divorce), depression and chronic stressors and academic stress, the authors discuss the findings of several investigations. From various physiological and psychological tests such as assays and behavioral assessments, the authors present a substantial amount of data supporting the proposition that psychological stressors can impair immune function. For instance, study participants suffering from the death of a loved one have poorer lymphocyte proliferation to mitogen stimulation than matched controls. Likewise, study participants who were divorced, suffering from depression or

chronic stress all had poorer immune function compared to controls. Kiecolt-Glaser and Glaser also reported the results of the effects of academic stress on the immune system. Again, a poorer immune system response such as decline in natural killer cell activity, T-lymphocytes, and mitogen responsiveness was documented.

Reflecting the general beliefs that have existed for centuries, these studies actually represent the general influence of psychological/emotional states on the immune system. It has been long thought that events perceived as harmful or unfavorable would affect the immune system adversely. Conversely, events perceived as uplifting or beneficial in nature would strengthen immune function. The studies presented in this literature review along with the majority of studies that have been published seem to support the effects of emotional or psychological states on the immune system. That is, negative events appear to impede the biological processes related to the immune system and positive events seem to stimulate it.

Parenthetically, there is yet another type of broad division that is far more subtle in the literature. The division comes from another group of scientist who espouse a more extreme point of view when talking about health and some of the causes of disease. This group of scientists can collectively be identified with the holistic/alternative medicine group. The focus is on the psychological as well as the physical in the individual. Attitudes/moods and states of consciousness which have a far less mundane quality can be as destructive as the micro-organisms that invade the body. Some of the techniques employed to heal the body relate to these more subtle conscious experiences. As a result of this, a

distinction in regards to conscious experiences can be made. Emotions, attitudes, moods can be thought of as behavioral and the more subtle, less mundane aspects of consciousness can be designated as psychological.

The relaxation response and meditation technique serve as an excellent example of this distinction or type of classification. The relaxation response is a technique in which a person sits quietly with eyes closed for 20 minutes. The person is instructed to breathe in a certain way and concentrate on one positive word. This is very similar to meditation with one exception. The individual who practices the relaxation response focuses on a mundane word oppose to a mantra for meditation. Although this is a subtle difference, it is a critical one for some scientists. Both techniques have been reported to alter physiological processes (Dienstrey, 1991).

To summarize, evidence which supports the psychological modulation of the immune function is becoming substantial. Empirical results have been cited in studies using subjects from the general population, the mentally ill and animals. Although there has been a great deal of research in this area, the investigation of how psychological/emotional states affect the body is still in its infancy. Scientist do not yet know to what extent the mind can affect the body. However, when one considers the fact that the immune system's ability to fight disease doubles when meditation is practiced only three times a week (Borysenko et al, 1990), one starts to wonder how powerful the mind or more specifically "consciousness" is.

Although there have been many literature reviews (Geiser, 1989; Kent, Coates, Pelletier, & O'Regan, 1989; Levy & Wise, 1987; Stern, 1988) there have been only one or two statistical analyses of the results of the studies performed. Therefore the objective of this research project is to perform a meta-analysis on human studies that look at the impact of psychological events on the immune system.

Meta-Analysis

A meta-analysis is a statistical integration of independent studies within a specific area of scientific investigation (Mullen, 1989). Whereas in a traditional primary analysis, the unit of analysis is the individual subject response, the unit of analysis in a meta-analysis is the independent statistical results. The procedures or techniques of the meta-analysis transform the independent statistical results into 2 common metrics: Z-scores and probability levels for significance levels and Fisher's Zs, product-moment correlations, and Cohen's d for effect sizes.

Thus meta-analysis is a collection of statistical procedures which has existed for decades (Mullen, 1989). Meta-analysis employs such techniques as derivation of mean effect sizes and combination of probability levels. These techniques allow the researcher to provide a set of numbers that summarizes an area of research.

Mullen (1989) explains that meta-analysis, like the traditional primary analysis, answers the same basic questions concerning central tendency, variability and prediction and explanation. That is, it seeks to identify the typical outcome, the typical differences from the

typical result and then tries to account for variability around the typical result.

In order to determine the central tendency of significance levels and effect sizes of a group of studies, the transformed outcome measures are, in a sense, combined. Meta-analysis uses statistical procedures such as the ones mentioned above, the derivation of mean effect sizes and combination of probability levels, to accomplish this.

In order to assess variability around the typical outcome, "diffuse comparisons" of significance levels and effect sizes are employed. Using chi-squared statistics, a researcher will be able to determine if the hypothesis tests are heterogeneous or homogeneous. If the diffuse comparison procedure yields a significant value, then the researcher can conclude that the tests were sampled from different populations.

In order to account for the variability around the typical outcome, focused comparison procedures are used. For this procedure, the researcher selects a set of characteristics germane to the area before the analysis occurs. These characteristics are then correlated with significance levels and effect sizes to determine which characteristic vary in a meaningful and predictable way (Mullen, 1989). The characteristics or predictors help in the understanding of the variability of a group of study outcomes. A researcher can analyze the characteristics of different study and try to understand the differences in terms of the characteristics of a study (Glass et al., 1984)

In this meta-analysis, 7 characteristics were chosen: publication date, population, validity, experimental situation, type of treatment, duration of treatment, and modulation of immune system. Given that this

is one of the first meta-analyses in the area, broad and general characteristics were selected for exploratory purposes. The selected characteristics or predictors represent some of the basic methodological and theoretical aspects that an investigator would first look at to assess an area.

For instance, a methodological predictor of import is validity. Given the nature of the investigation, it is very important to determine if the modulation of the immune system is due to psychological events or external factors such as illness, antibiotics or other medications. This external event would allow a false conclusion to be rendered.

The next methodological predictor is experimental situation. Laboratory settings have been cited often for being artificial in nature. This could impede the independent variable or psychological event from having an effect. Conversely, naturalistic settings can be compromised and hence create an effect which is not a result of the study manipulation.

Another methodological variable that was selected was population. This predictor was chosen to assess the different types of subjects selected for the studies. Specifically, it assessed the use of students and the use of individuals from the general population. Finally, the last methodological predictor was publication date. This predictor is found in most meta-analyses. It helps to evaluate an area of investigation from a historical perspective.

In terms of theoretical or substantive predictors, type of treatment was selected. Central to the research in this area is the psychological event. In the literature, there is a broad array of

psychological events that have been investigated. In the studies that were selected for this meta-analysis, the following represent the types of psychological events that were investigated: marital stress, stress of a family caregiver whose relative suffers from a major disease, academic stress, major life changes such as a loss of a job, commonplace stress such as the demands of a job, acute laboratory stress which is brought on by complex problem solving tasks, social support, music-assisted imagery, humorous videotapes, daily relaxation, and biofeedback-assisted relaxation. However, in most categories of events, there are relatively few in number. Therefore, this predictor was broken down into positive and negative categories.

Related to this substantive predictor was the length of time of the psychological event. Again, this predictor was broken down into two broad categories. With this predictor, it seemed important to assess the temporal aspects of the treatment. The last substantive predictor was the direction of effect on the immune system that the psychological event had. Specifically, this predictor evaluated if there was a increase, no change and decrease in immune function.

To conclude, the advantage of a meta-analysis is that it affords a more precise and objective review of the literature. Because this type of review ensures that the judgments be made "public and explicit," it is perceived as less subjective than a narrative review. Since the mid seventies, the social sciences have been employing meta-analysis as a viable statistical procedure (Glass et al, 1984). It has grown tremendously in popularity.

Hypotheses

The hypotheses of the study are: 1) psychological and behavioral factors are related to immune functioning. The prediction is that "positive events" will increase the immunological ability and "negative events" will decrease its ability. 2) Both psychological and behavioral factors are related to immune functioning. The prediction is that combined psychological/behavioral interventions will increase immunological function more than behavioral interventions alone.

CHAPTER II

Method

Sample of Studies

Computer-based search procedures were used to identify potential studies. Four data bases were searched, exhaustively: Psychlit (1967 to 1994); Educational Resources Information Center (1966 to 1994); Dissertation Abstracts International (1961 to 1994); and Medline (1970 - 1994). To expedite the exploratory process, the following keywords were used to find potential studies: psychoneuroimmunology, psychoimmunology, psychoneuroendocrinology, psychosomatic, consciousness, immunoglobulin, immunoglobulins, IgA, IgM, IgG, lymphocytes, natural killer cells, innate and acquired immunity, T cells, B cells, phagocytic, immunity, antibodies, mind-body, holistic, visualization, guided visualization, imagery, PNI, meditation, relaxation response, biofeedback, and hypnosis. In addition to the computer-based search procedures, potential studies were identified by reviewing reference lists of review articles, books, and chapters and the reference lists of all located studies.

When all potential studies were identified, each was reviewed in order to select legitimate studies appropriate for the meta-analysis. Criteria for the selection of studies were: a) a study displaying experimental control that included randomization of individual subjects to comparison groups; b) a psychological or behavioral event (biofeedback, relaxation techniques, guided visualization, etc.), was the independent variable and was manipulated in some experimental fashion; c) an immunological measure (i.e., lymphocytes, natural killer cells, neutrophils, etc.) was the dependent measure; d) dependent measures were a direct response to the psychological modulation; and e) studies that used subjects with a biologically-based clinical psychiatric diagnosis were excluded.

In all 47 studies were identified as potential studies for the meta-analysis. However, only 34 met the selection criteria and were used in the statistical analysis.

Study Characteristics

In order to assess potential sources of variability, seven study characteristics were used as predictors in this study. There were four methodologic predictors and four substantive predictors. Predictors were assigned a numeric value which displayed in Table 1. The following information was extracted from each study and coded.

A) Date of Publication. This predictor was the publication date of the journal article. The year was recorded as the numeric value.

B) Type of Population. This predictor characterized the source from which the subjects were recruited. The population was broken down into 3 categories: student (coded 1), general (coded 2) and a combination of student and general (coded 3). The first category was student. A sample was recorded in this category if the subjects were enrolled in an academic program. This included undergraduates, graduates, medical and dental students. The second category was general. Subjects recruited from general community populations were coded in this category. The third category included subjects who were recruited from both academic and community settings.

C) Validity. This predictor assessed the overall internal validity of the study i.e. assessing the effectiveness of the independent variable on the dependent variable. Special consideration was given to two protocols regarding one of the seven threats to internal validity, testing or reactive measures. The first was the experimenter's controlling for the medical history of the subject. This included excluding subjects who were ill or recently ill and/or taking medication that impacted on the immune or endocrine systems. The second was the

experimenter collecting assays during mid to late mornings hours to control for variability due to circadian rhythms of hormonal and immunological substances. If the experimenter controlled for these two along with other threats to internal validity, the study was considered to have high validity (coded 3). If the experimenter only controlled for one of the two special considerations, the study was considered to have medium validity (coded 2). If the experimenter did not control for either, the study was considered to have low validity (coded 1).

D) Experimental Situation. If the study was an artificial situation, i.e., the deliberate manipulation of an independent variable on the dependent variable in a laboratory setting, it was considered a true experiment and coded as a 1. If the study was designed around a natural occurring independent variable such as an examination period for students it was considered a naturalistic experiment and coded as a 2.

E) Type of Treatment. This predictor identified the general type of intervention that was received by subjects in the experimental group. This was divided into two groups: 1) a positive event, and 2) a negative event. A positive event was identified as a situation that improved or uplifted in some emotional/psychological way a person's disposition. Examples of this would be social support, visualization, humorous movie, music-assisted imagery. A negative event was identified as a situation in which the subject experienced some form of emotional or psychological strain or pressure.

F) Duration of Treatment. In order to evaluate the temporal factor further, this predictor assessed the specific length of time that subjects were exposed to the intervention. The predictor was broken down into two categories: (1) single or multiple sessions or an ongoing event occurring within a month or (2) multiple sessions or an ongoing event occurring for more than a month. This included prolonged situations lasting a substantial period of time.

G) Modulation. This category was designed to assess the overall change in the immunological measures. It was broken down into three categories: increase (coded 1), no change (coded 2) and decrease (coded 3).

Table 1

<u>Predictors</u>	<u>Predictors Values</u>		
	1	2	3
Publication Date			
Type of Population	Student	General	Mixed
Validity	Low	Medium	High
Experimental Situation	Artificial	Natural	
Type of Treatment	Positive	Negative	
Duration of Treatment	Less than Month	More than Month	
Modulation	Increase	No Change	Decrease

Procedure

After a computer-based search identified all potential articles, the articles were retrieved and assessed for being appropriate for the meta-analysis. Inclusion was based on criteria which were established previously. If the study met the requirements, predictors were coded for the individual studies and entered into a data file along with the statistical tests. The majority of the studies had multiple immunologic measures being assessed in the experimental condition. Hence immunologic measures were grouped by type of cell. In all, 12 separate immunologic measures were identified as dependent measures. They were: neutrophils, phagocytotoxic cells, natural killer cells, large granular lymphocytes, lymphocytes, B lymphocytes, immunoglobulin A(IgA), immunoglobulin G(IgG), immunoglobulin M(IgM), T lymphocytes, suppressor/cytotoxic lymphocytes, and helper/inducer lymphocytes. For a second level of

analysis, the 12 dependent measures were grouped according to the specific type of immunity, i.e. innate vs. acquired. Acquired is broken down into humoral vs cellular immunity. Data were analyzed using the BASIC Meta-Analysis program (Mullen 1989).

Statistical Analysis

Meta-analyses for the individual immunological groups and immune system group were performed. In order to do this, the two principal outcome measures of the statistical tests, significance levels and magnitude of effect, were transformed into common metrics. For significance levels, Z scores and probability values were calculated. For the second outcome measure, magnitude of effect or effect size, product-moment correlation coefficient r , Fisher's Z and Cohen's d were reported. Subsequent to transforming the data, analyses were performed to determine the central tendency and variability for each sub-study. In order to determine the central tendency, a procedure that combined the data was used. To determine variability, a diffuse comparison procedure was used. A focused comparison of significance levels and effect sizes was used to answer questions concerning variability.

CHAPTER III

Results

The statistics that were reported for each hypothesis test were transformed into common metrics: Z scores and one-tailed probability levels for the significance level and product-moment correlation's, Fisher's Zs and Cohen's d for the effect size. Along with the common metrics for significance level and effect size, the coefficient of determination, r^2 , was calculated and also reported.

As reported previously, hypothesis tests were grouped according to the type of dependent measure for which an independent meta-analysis was performed. Tables 2 - 13 represent the individual sub-studies of the different immunologic or dependent measures. The individual tables contain individual hypothesis tests and corresponding statistical transformations which are numbered by citation in appendix A. In all, 12 immunologic measures were used as dependent measures in the studies that were selected. The tables are arranged in terms of type of immunologic measure. Tables 2 - 6 represent the cells of innate immunity. Tables 7 - 10 represent the B lymphocyte cells in humoral immunity and tables 11 - 13 represent the T lymphocyte cells in cellular immunity. In appendix B, tables which contain the predictors and their values are displayed. The order of those tables coincides with the order of tables in this section.

In Table 2, the calculations of the common metrics for the neutrophil cells sub-study are reported. The Z scores and associated p values for this sub-study indicate there are significant differences between compared conditions in the two studies. In terms of the common metrics for effect size, the results show medium and large effect sizes.

Table 2

Primary Study Results for Neutrophils

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
24.	t(18) = 2.30	20	+	2.12	.0169	0.52	.476	.227	1.08
21.	p = .016	31	+	2.14	.0160	0.41	.385	.148	.83
27.	t(28) = 1.93	30	+	1.85	.0319	0.36	.343	.117	.73

Note. df = degrees of freedom; N = number of subjects in study; DOE = direction of effect; Z = z score; p = probability value; zFisher = Fisher's Z score; r = product-moment correlation; r² = coefficient of determination; d = Cohen's d.

In Tables 3, 4, and 5 similar results are shown for phagocytotoxic cells, large granular lymphocytes, and lymphocytes sub-studies. All Z scores and associated p values represent that there are differences between compared conditions and the common metric for the magnitude of effect or effect sizes range from medium to large with one exception.

Table 3

Primary Study Results for Phagocytotoxic Cells

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
26.	X ² (1) = 3.86	41	+	1.96	.047	0.32	.307	.094	.64
26.	F(1,21) = 11.11	23	+	2.81	.025	0.80	.665	.442	1.78
25.	p = .05	8	+	1.64	.050	0.66	.582	.388	1.43

Table 4

Primary Study Results for Large Granular Lymphocytes

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
24.	F(1,20) = 19.24	22	+	3.63	.00044	0.87	.700	.490	1.96
5.	F(1,39) = 6.58	41	+	2.44	.00714	0.40	.379	.144	.82

Table 5

Primary Study Results for Lymphocytes

Study Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
27. $t(28) = 2.11$	30	+	2.01	.0220	0.39	.37	.137	.80
34. $F(1,22) = 5.32$	24	+	2.16	.0155	0.47	.44	.194	.98
21. $p = .05$	31	+	1.64	.05	0.30	.30	.080	.62
33. $r = .13(254)$	256	+	2.08	.0188	0.13	.13	.017	.26

Table 6

Primary Study Results for Natural Killer Cells

Study Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
15. $F(1,50) = 1.27$	52	+	1.11	.132	0.14	.137	.019	.28
9. $F(1,48) = 5.59$	50	+	2.29	.0111	0.33	.323	.104	.68
9. $F(1,61) = 7.39$	63	+	2.63	.0043	0.34	.329	.108	.70
9. $F(1,77) = 2.54$	79	+	1.58	.0575	0.18	.179	.032	.36
14. $F(1,68) = 9.87$	70	+	3.02	.0012	0.37	.356	.127	.76
17. $F(1,41) = 4.99$	43	+	2.16	.0155	0.34	.329	.108	.70
8. $r(35) = .28$	37	+	1.68	.047	0.29	.280	.078	.58
2. $F(1,21) = 7.91$	23	+	2.56	.0052	0.58	.523	.273	1.22
13. $F(1,27) = 3.98$	29	+	1.91	.0281	0.38	.358	.128	.77
19. $r(8) = -.17$	10	+	1.81	.0352	-0.17	-.170	.029	.34
23. $r(8) = -.06$	10	+	0.16	.434	-0.06	-.060	.003	.12
5. $F(1,39) = 8.14$	41	+	2.70	.0034	0.44	.416	.173	.91
7. $r = -.21(18)$	20	+	0.94	.174	-0.21	-.210	.044	.43
23. $r(8) = .14$	10	+	0.38	.350	0.14	.140	.019	.28
1. $F(1,41) = 4.99$	43	+	2.15	.0154	0.34	.320	.106	.69
30. $F(1,18) = 16.39$	20	+	3.69	.0001	0.60	.530	.286	1.26
16. $F(1,158) = 3.73$	90	+	1.92	.0276	0.15	.150	.020	.31
24. $F(1,20) = 16.95$	22	+	3.46	.0003	0.82	.680	.460	1.84
29. $p < .05$	45	+	1.64	.05	0.25	.240	.060	.50
22. $t(18) = 2.32$	20	+	2.13	.0162	0.52	.479	.230	1.09

In Table 6, the calculations of the common metrics for natural killer cells are reported. The Z scores and associated p values for the sub-study indicate that there are not significant differences in 5 of the twenty individual studies. The effect sizes, in this dependent measure, range from small to large.

In Tables 7, 8, 9, and 10 the common metrics indicate that a number of individual studies for immunoglobulin A, G, M, and B lymphocytes sub-studies show significant differences between compared conditions with the exception of five individual hypothesis tests. In addition, the magnitude of effect ranged from small to large with the exception of the two individual hypothesis tests.

Table 7

Primary Study Results for IgA

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
14.	F(1,42) = 6.05	44	+	2.36	.0091	0.37	.355	.126	.76
3.	t(8) = -2.26	10	+	1.92	.0272	0.73	.624	.39	1.60
18.	t(8) = 2.30	10	+	1.95	.026	0.74	.630	.398	1.63
28.	F(1,14) = 21.14	16	+	3.52	.0002	1.03	.776	.601	2.45
6.	F(1,39) = 22.46	41	+	4.18	.00001	0.70	.604	.365	1.51
10.	F(1,28) = 23.72	30	+	4.10	.00002	0.82	.677	.459	1.84
6.	F(1,39) = 6.51	41	+	2.43	.00739	0.40	.378	.143	.82
4.	r(10) = .56	12	+	1.89	.0293	0.63	.560	.314	1.35
4.	r(10) = .35	12	+	1.11	.132	0.36	.350	.122	.75
20.	t(18) = 3.68	20	+	3.13	.0009	0.78	.650	.429	1.73
31.	F(1,28) = 6.83	30	+	2.45	.0071	0.48	.443	.196	.99

Table 8

Primary Study Results for IgG

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
14.	F(1,35) = 1.43	37	+	1.18	.120	0.20	.198	.039	.40
32.	t(48) = 2.25	50	+	2.18	.014	0.32	.309	.095	.65
6.	F(1,39) = 20.42	41	+	4.00	.0284	0.67	.586	.344	1.45

Table 9

Primary Study Results for IgM

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
14.	F(1,42) = 2.61	44	+	1.58	.0568	0.25	.241	.058	.50
6.	F(1,39) = 4.34	41	+	2.02	.0219	0.33	.316	.100	.67

Table 10

Primary Study Results for B Lymphocytes

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
17.	F(1,40) = 4.16	42	+	1.98	.024	0.32	.307	.094	.64
22.	t(18) = 2.43	20	+	2.22	.0129	0.54	.497	.247	1.14
1.	p = .50	44	-	-1.09	.50	0*	0	0	0
24.	p = .50	23	-	-1.08	.50	0	0	0	0
22.	t(18) = 2.36	20	+	2.17	.0149	0.53	.486	.236	1.11

In the last group of dependent measures, cellular immunity cells or T cells, seven individual hypothesis tests failed to indicate a significant difference between compared conditions. Magnitude of effect displayed a similar pattern to the humoral immunity cells.

Table 11

Primary Study Results for T Lymphocytes

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
13.	F(1,31) = 4.08	33	+	1.94	.0261	0.36	.341	.116	.73
2.	F(1,21) = 5.86	23	+	2.24	.0123	0.51	.467	.218	1.06
1.	p = .50	44	-	-1.08E-07	.50	0	0	0	0
16.	F(1,142) = 9.80	90	+	3.07	.0011	0.26	.254	.064	.52
11.	F(1,18) = 6.17	26	+	2.27	.0116	0.56	.505	.255	1.17
24.	p = .50	22	-	-1.08E-07	.50	0	0	0	0
29.	p < .05	45	+	1.64	.05	0.25	.24	.06	.51
15.	F(1,62) = 4.87	64	+	2.16	.0155	0.28	.270	.073	.56

Table 12

Primary Study Results for Helper/Inducer Lymphocytes

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
1.	p = .50	44	-	-1.08E-07	.5	0	0	0	0
16.	F(1,142) = 6.40	90	+	2.50	.006	0.21	.208	.040	.42
24.	p = .50	23	-	-1.08E07	.5	0	0	0	0
29.	p < .05	45	+	1.64	.05	0.25	.240	.060	.51
15.	F(1,62) = 18.49	64	+	4.00	3.09E-05	0.52	.479	.229	1.09

Table 13

Primary Study Results for Suppressor/Cytotoxic Lymphocytes

Study	Statistic(df)	N	DOE	Z	p	zFisher	r	r ²	d
15.	F(1,62) = 1.12	64	+	1.09	.136	0.14	.139	.019	.28
27.	F(1,31) = 1.07	33	+	1.02	.154	0.18	.183	.033	.37
1.	p = .50	44	-	-1.08	.5	0	0	0	0
30.	F(1,18) = 4.98	20	+	2.07	.0193	0.50	.466	.217	1.05
11.	F(1,17) = 10.25	19	+	2.79	.00263	0.71	.613	.376	1.55
24.	F(1,20) = 4.83	22	+	2.05	.0199	0.47	.441	.194	.98
29.	p < .05	45	+	1.64	.05	0.25	.245	.060	.51
16.	F(1,143) 39.67	90	+	5.91	2.14E-09	0.50	.466	.217	1.05
22.	t(18) = 2.75	20	+	2.48	.00616	0.61	.544	.296	1.30

In conjunction with these results, the coefficient of determination, r^2 , is also reported. The statistic represents the percent of variance in the dependent variable accounted for by the independent variable. The lowest overall percent of variability accounted for was .003. The highest overall percent of variability accounted for was .601.

Tables 13 and 14 represent the combination of significance levels and effect sizes, unweighted and weighted, respectively for each sub-study. The unweighted combination of significance levels represent the procedure in which individual studies contribute an equal amount to the statistical analysis. The weighted combination of significance levels and effect sizes represents studies being weighted by sample size. The combination of significance levels and effect sizes yields results of central tendency for each sub-study.

In terms of the first outcome measure(unweighted), the sub-studies of natural killer cells, immunoglobulin A, suppressor/cytotoxic cells

and T lymphocytes display the strongest Z scores and associated probability levels (Table 14). The weakest sub-studies are immunoglobulin M, B lymphocytes, neutrophils, and helper/inducer lymphocytes. However, in all general combinations of hypothesis tests, all sub-studies demonstrated a statistically significant difference between comparison groups.

Table 14

General Combination of Hypothesis Tests - Unweighted

Dependent Measure	N	Z	p	zFisher	r	r ²	d	FS
1. Neutrophils	3	3.53	.000204	.427	.403	.162	.88	11
2. Phagocytotoxic	3	3.71	.000105	.595	.533	.284	1.26	12
3. N K C	20	8.93	7.87E-18	.289	.281	.078	.58	570
4. L G L	2	4.29	8.78E-06	.634	.561	.314	1.35	12
5. Lymphocytes	4	3.95	3.95E-05	.324	.314	.098	.66	19
6. IgA	11	8.77	2.37E-17	.642	.566	.321	1.37	302
7. IgG	3	4.26	1.02E-05	.397	.378	.143	.82	17
8. IgM	2	2.53	.00568	.286	.278	.077	.58	3
9. B Lymphocytes	5	2.85	.00217	.279	.272	.073	.56	10
10. T Lymphocytes	8	4.99	3.11E-07	.273	.266	.071	.55	74
11. Suppressor	9	6.35	.000154	.376	.359	.129	.77	125
12. Helper	5	3.64	.000134	.197	.194	.038	.40	19

Note. FS = fail safe number.

In addition to the transformed data, fail-safe numbers were calculated. A fail-safe number is the estimated number studies that would nullify the results in the combination procedure. The larger number indicates the robustness of the results. In general, the sub-studies with a greater number of hypothesis tests are more robust.

In Table 15, the sub-studies are weighted by sample size. The results are similar, but not identical. The strongest Z scores and associated p values are the same as the ones in the unweighted analysis of general combinations. However, the weakest sub-studies are B lymphocytes, immunoglobulin M, lymphocytes, and phagocytotoxic cells.

Table 15

General Combination of Hypothesis Tests - Unweighted

Dependent Measure	N	Z	p	zFisher	r	r ²	d
1. Neutrophils	3	3.46	.000269	.416	.393	.155	.86
2. Phagocytotoxic	3	3.10	.000967	.479	.446	.199	1.00
3. N K C	20	7.54	8.41E-14	.239	.234	.055	.48
4. L G L	2	3.87	5.39e-05	.563	.510	.260	1.19
5. Lymphocytes	4	2.67	.00382	.193	.191	.036	.39
6. IgA	11	8.44	2.16E-16	.599	.536	.288	1.27
7. IgG	3	4.26	1.02E-05	.397	.378	.143	.82
8. IgM	2	2.53	.00568	.286	.278	.077	.58
9. B Lymphocytes	5	2.41	.00794	.234	.229	.052	.47
10. T Lymphocytes	9	5.09	1.86E-07	.259	.253	.064	.52
11. Suppressor	9	6.54	5.00E-11	.331	.319	.102	.67
12. Helper	5	4.29	8.68e-06	.239	.235	.055	.48

In terms of the second outcome measure, magnitude of effect, there is a consistent ranking in the two general combinations of hypotheses tests. Immunoglobulin A has the strongest effect size in both analyses. The remaining effect sizes are similar in ranking although not identical. The majority of effect sizes are medium to large in both

analyses. Mullen (1991) indicates that small, medium and large effect sizes correspond to values of .20, .63, and 1.15, respectively. Cohen cites value of .20, .50, and .80 for small, medium, and large effect sizes, respectively. However, in general, the weighted procedure did not contribute greatly to the general combination of hypothesis tests procedure.

Tables 16 and 17 represent the immunologic measures, grouped according to innate and acquired immunity. Acquired immunity is subdivided into two groups: Humoral Immunity(B cells) and Cellular(T cells). The two tables represent unweighted and weighted general combinations of hypothesis tests in the two types of immunity.

Table 16

General Combination of Hypothesis Tests - Unweighted

Dependent Measures	N	Z	<u>Significance Effect Sizes</u>					FS
			p	zFisher	r	r ²	d	
1. Innate Immunity	38	11.04	6.95E-24	.334	.322	.104	.68	1590
2. Humoral Immunity	21	10.13	2.55E-21	.487	.452	.204	1.01	776
3. Cellular Immunity	22	8.64	5.49E-17	.298	.289	.084	.61	585

Table 17

General Combination of Hypothesis Tests - Weighted by Sample Size

<u>Significance Effect Sizes</u>							
Dependent Measures	N	Z	p	zFisher	r	r ²	d
1. Innate Immunity	38	8.62	6.40E-17	.293	.285	.081	.59
2. Humoral Immunity	21	9.57	1.11E-19	.441	.414	.172	.91
3. Cellular Immunity	7	9.14	1.93E-18	.284	.276	.074	.58

The unweighted and weighted analyses have different results for the first outcome measure. Innate Immunity has the strongest Z score and associated p value, yielding the most significant difference between the conditions in the unweighed procedure. However, Innate Immunity is the weakest in the weighted procedure. In terms of the magnitude of effect, The results are more consistent. Humoral Immunity exhibits the strongest effect size and Cellular Immunity demonstrates the weakest effect size in both procedures.

Tables 18 and 19 represent the results of the diffuse comparison of significance levels and effect sizes.

Table 18

Diffuse Comparisons of Significance Levels

<u>Dependent Measure</u>	<u>X²</u>	<u>df</u>	<u>p</u>
1. Neutrophils	0.05	(2)	.974
2. Phagocytosis	0.72	(2)	.697
3. N K C	15.74	(19)	.675
4. LGL	0.69	(1)	8.78E-06*
5. Lymphocytes	0.15	(3)	.984
6. IgA	6.05	(10)	.534
7. IgG	9.59	(2)	.477
8. IgM	0.09	(1)	.006*
9. B Lymphocytes	5.46	(4)	.244
10. T Lymphocytes	8.55	(7)	.381
11. Suppressor	21.91	(8)	.005*
12. Helper	11.71	(4)	.0197*

* p < .05

In Table 18, the unweighted diffuse comparison of significance levels show that 4 sub-studies demonstrate significant variability around the typical outcome. The sub-studies are Large Granular Lymphocytes, Immunoglobulin M, Suppressor/Cytotoxic and Helper/Inducer Lymphocytes. Table 19 represents the diffuse comparison of effect sizes. The results of this analysis yield significant results for Natural Killer Cells, Large Granular Lymphocytes and Immunoglobulin M.

Table 19

Diffuse Comparisons of Effect Sizes

<u>Dependent Measure</u>	<u>X²</u>	<u>df</u>	<u>p</u>
1. Neutrophils	0.28	(2)	.871
2. Phagocytosis	2.52	(2)	.283
3. N K C	45.91	(19)	.0005*
4. LGL	2.77	(1)	8.78E-06*
5. Lymphocytes	4.02	(3)	.259
6. IgA	9.65	(10)	.472
7. IgG	4.46	(2)	.107
8. IgM	0.13	(1)	.006*
9. B Lymphocytes	6.76	(4)	.149
10. T Lymphocytes	7.58	(7)	.475
11. Suppressor	14.83	(8)	.062
12. Helper	8.46	(4)	.076

Diffuse comparisons analyses were done on the immunologic measures, grouped according to innate and acquired immunity. The results of the analyses indicated no significant variability around the typical outcome either for significance levels or effect sizes. Similar results were obtained when a weighted diffuse comparison was performed.

In order to determine if predictors covaried significantly with effect sizes, focused comparisons of effect sizes were performed. As with the general combinations, two levels of analyses were done. The first was the focused comparison of the individual dependent measures. The second was the focused comparison of the general groups of dependent measures i.e. innate, humoral, and cellular immunity.

In terms of the first analysis of the dependent measures, lymphocytes, natural killer cells, large granular lymphocytes, immunoglobulin G and M, suppressor/cytotoxic cells, helper/inducer cells, and B and T lymphocytes were identified as having predictors that covaried significantly with the outcome measure, effect size. For the other dependent measures, phagocytotoxic cells, neutrophils, and immunoglobulin A, the predictors did not covary significantly with effect sizes.

Table 20

Focused Comparisons of Effect Sizes: Innate Immunity

	<u>Predictors</u>						
	1	2	3	4	5	6	7
Neutrophils							
Phagocytotoxic							
Lg. Granular Lymphocytes	.99*	1.00*		-1.00**			-1.00**
Lymphocytes				-.87*			
Natural Killer Cells	.24**	.39**	-.13*	-.38**			-.34*

Note. Predictor 1 = Publication Date; 2 = Type of Population; 3 = Validity; 4 = Experimental Situation; 5 = Type of Treatment; 6 = Duration of Treatment; 7 = Modulation.

* $p < .05$

** $p < .001$

Table 21

Focused Comparisons of Effect Sizes: Humoral Immunity

	<u>Predictors</u>						
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>
IgA							
IgG		.96*	-.29*	-.97**	-.97**	-.29**	-.68**
IgM				-1.00*	-1.00*		-1.00*
B Lymphocytes				.94*		.88*	-.94*

Table 22

Focused Comparisons of Effect Sizes: Cellular Immunity

	<u>Predictors</u>						
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>
T Lymphocytes			.58**	.72**	-.46**	.75**	
Helper	-.65**		.56**	.79**		.85**	-.38**
Suppressor		.28**	.54**	.03**		.16**	.55**

The second level of focused comparisons of effect sizes were performed on the three general groups of dependent measures. For the focused comparison on the innate immunity group, Publication Date and Type of Treatment predictors did not covary with effect size. For humoral and cellular immunity, all predictors with the exception of Date of Publication covaried significantly with effect size.

Table 23

Focused Comparisons of Effect Sizes: Innate and Acquired Immunity

	<u>Predictors</u>						
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>
Innate Immunity		.30*	-.17*	-.33*		-.21*	-.31*
Humoral Immunity		-.17*	.24**	-.13**	-.40*	.29*	-.10*
Cellular Immunity		-.12**	.51**	.43**	-.20**	.50**	.36**

CHAPTER IV

Discussion

As the studies in the psychoneuroimmunology domain congeal and the connection between emotional states and biological processes becomes even more self-evident, greater scientific scrutiny will be imperative. The statistical review of these studies in this dissertation is one preliminary step towards this scientific scrutiny

The objective of this study was to do a quantitative review of the literature in the area of psychoneuroimmunology. The results of this quantitative review provided a set of numbers which summarized the body of research in a succinct way. The statistical integration provided information about the general analytic questions of central tendency, variability, and prediction. The question of central tendency was answered by the combination procedure of significance levels and effect sizes. The combination procedures illuminated the typical study outcome. The question of variability within groups was answered by the diffuse comparison procedure. The question of explanation and prediction was ascertained by the focused comparison procedures.

In terms of the typical outcome or central tendency for this area of investigation, analyses do indicate reliable relationship between the independent and dependent variables or significant differences between compared conditions. When individual hypothesis tests were analyzed according to immunological group, i.e. sub-studies, relatively strong results were achieved for the combinations procedures. The combination procedures, unweighted and weighted, which illuminates central tendency, i.e. the typical outcome, supports the psychological modulation of the immune system.

The second outcome measure, effect size, was also relatively strong. These results which pertain to magnitude of effect, unweighted

and weighted, further support the efficacy of the psychology modulation of the immune system. The majority of effect sizes or d scores fall in the medium to large effect range for sizes if one uses Cohen's criteria for small(.20), medium(.50), and large(.80) scores.

When sub-studies were grouped by immune system classification, i.e. innate vs. acquired, the overall Z scores in the unweighted and weighted combination procedures grew stronger. However, the magnitude of effect in the unweighted and weighted combinations, was diminished. This is a result of the effect size being equal to the significance level divided by the study size (Mullen, 1989). The larger the denominator or sample size, the smaller the effect size.

Based on the results of the combination analyses alone, speculation about which immunologic measures were more sensitive to psychological intervention might be attempted. Given that the immunologic measures perform different or specific functions, some maybe more readily available or sensitive to manipulation. For example, the suppressor T cells regulate other immunologic cells such as the natural killer cells or the helper T cells stimulate other immunologic cells. It maybe the case that a psychological intervention may have greater influence on one type of immunologic measure than another because of its functional and molecular structure.

However, although the general combination procedures are used to determine the typical outcome, the results of these procedures may not portray correctly the typical result. Hence, it would be premature to try to guess at the sensitivity of an immunologic measure or the impact of a psychological intervention. To assess variability within the various groups, diffuse comparisons were executed. These analyses indicated that some of the sub-studies were not a homogeneous group of outcome measures.

The large granular lymphocyte sub-study for example had a significant diffuse comparison of significance level. Significant diffuse comparisons were identified in the immunoglobulin M, suppressor and helper T cells sub-studies. For diffuse comparisons of effect sizes, large granular lymphocyte, natural killer cells, and immunoglobulin M were the only significant results. In general, the significant diffuse comparisons clouds the effects of the psychological impact on a dependent measure. Although relatively few sub-studies had significant diffuse comparisons, it would still hinder any further speculation about the sensitivity of the dependent measures.

In order to try to understand the variability, focused comparisons of effect sizes were performed. As Mullen (1989) states, a focused comparison of the outcome measure identifies predictors that covary significantly with the measure. The predictors that covary with the outcome measure gives insight into sub-studies outcomes. Predictors identify potential sources of variability. It is with the assistance of the focused comparisons analysis that the meta-analysis truly excels and becomes an instructive research tool. It can shed light on the nature of the area under investigation and direct future research.

For instance, by reviewing the focused comparisons for the major immunity groups, the results would suggest that experimental designs which have innate immunity measures as dependent measures should be conducted primarily in laboratory settings. Stronger/more significant effect sizes were associated with laboratory settings. For these studies, laboratory settings also seem to be stronger in the humoral immunity group, although the correlation was weak. Conversely, for acquired immunity dependent measure, a natural setting seemed to be the optimal setting.

Related to the experimental setting, the duration of treatment covaried significantly with all three groups. Whereas innate immunity

has stronger effect sizes with a shorter duration of time, both acquired immunity groups yielded stronger results with longer treatment. The results for this predictor may speak to the nature of the two categories of immunity, i.e. innate vs. acquired. Being the first line of defense against foreign invaders, innate immunity be responsive only in a short time period. If a foreign invader remains around long enough than perhaps the second line of defense, acquired immunity is activated and innate immunity mechanisms wane. This scenario parallels the results of the focused comparisons for this predictor.

The predictor, type of treatment, covaried significantly with acquired immunity groups, only. In both cases, negative exposure had consistent result. This may be due to the fact that negative situations were less contrived than positive ones. It may also be the case that a threatening situation has a greater effect on the psyche than a favorable situation.

In terms of the nature of the population, it appears that innate and acquired immunity differentiates themselves, again. For innate immunity, non-student populations were significant in the focused comparisons. For acquired immunity, student populations had stronger effect sizes.

The last predictor, validity, covaried significant in all groups. The most notable result, however, is a negative correlation in the innate immunity group. This would indicate that studies with little experimental control displayed a greater effect. This calls into question what was modulating the immune system. The effects of the independent variable are compromised by this result. One could say that the modulation was a result of an external variable such as medication or illness. However, in the acquired immunity groups, high validity correlated significantly with stronger effect sizes.

To conclude, the results of the focused comparisons analyses for this meta-analysis indicated that several predictors covaried significantly with effect sizes. Although the statistical application of this procedure is limited, the procedure is useful in identifying potential informative predictors. These predictors can assist in accounting for variability in the results of a study. The procedure provides a meaningful starting place to begin to understand the event under investigation. The point is particularly salient in light of the views of two prominent researchers in the area, Robert Ader and Nicholas Cohen. In a literature review article, Ader and Cohen (1991) espoused the point that although there is a different relationship between psychological events and physiological processes which are mediated by the nervous system, the relationship is not fully understood because there are inconsistencies with the results. This maybe a result of smaller parameters such as the predictors that were used in this meta-analysis being different while the larger parameters, i.e. the event and effect remain constant. That is, the homeostasis of the immune system is altered as a result of a psychological event.

Finally, the prediction that positive events strengthen immune function and negative events weaken it was confirmed when a contingency coefficient, $C = .42$ was significant at the .01 level. This was accomplished by looking at the relationship between the treatment and modulation predictors. This supported the first hypothesis. In terms of the second hypothesis, it was determined that the distinction between behavioral and psychological was too discrete for this area of investigation at this time. The number of "psychological" interventions was nonexistent for all intensive purposes.

However, the analyses for this research project were able to quantify and verify the relationship between psychological events and

physiological processes. It further substantiated the importance of the behavioral/psychological component in health and illness.

For decades, the immune system was thought to be "fundamentally self-regulating and autonomous" (Dienstrey, 1991). This characterization can be found throughout the early literature in immunology. It has been only over the last few decades that this perception has begun to change and change dramatically. During this time, scientists have been investigating and demonstrating the effect of external forces that exist within the body which serve to modify the responses of the immune system. These external forces spanning from neuropeptides to behavior and psychological states can start to be considered legitimate biological modifiers. The studies that were reviewed and analyzed in this dissertation represent only a portion of work in this relatively new and exciting field of psychoneuroimmunology. The literature, for example, in the sub-human domains has greater breadth and depth than in any other area in psychoneuroimmunology.

As it was mentioned, previously, one of the profound implications of this research domain is that it allows us to look at diseases in a different way. It possibly can facilitate greater insight into some of the complex diseases that confront us. Neoplasia, for instance, is a disease that may be under the purview of these implications.

Neoplasia or cancer is a disease (or diseases) in which cells multiply and spread without any regulatory control and evolve into a malignant tumor (Kunz, 1982). According to the research, the immune system is a significant factor in the relationship between the host and the tumor (Benjamini & Leskowitz, 1989). According to Benjamini and Leskowitz (1989), humoral and cellular immune effector mechanisms have the ability to kill suspended tumor cells. Natural killer cells, suppressor/cytotoxic T lymphocytes, macrophages, phagocytic cells, IgM and IgG antibodies are all capable of killing tumor cells. This

relationship is solidified by the evidence that tumors occur more frequently in immunosuppressed individuals. Hence, these individuals are at greater risk for cancer (Benjamin & Leskowitz, 1989).

Similarly, in the psychoneuroimmunology literature, the connection between immunity and tumors has also been confirmed. However, in the psychoneuroimmunologic paradigm, stress becomes a deliberate and critical component in the equation. The literature supports that stress can alter the incidence and development of experimental tumors in animals (Shavit, 1990). Given the critical role of cellular and humoral immunity in neoplasia and the influence of emotional states on cellular and humoral immunity, one can start to understand the profound implications of psychoneuroimmunology research. From these relationships, a foundation is laid for a potentially critical factor in an elusive complex disease, which is the second leading cause of death (Copple, 1995).

The significance of the relationships are even starting to be recognized by those most involved in somatic function, medicine. For example, in an article entitled, *Neuroendocrine-Immune Interactions* which appeared in the New England Journal of Medicine (Reichlin, 1993), a technical explanation of the relationship between immune, endocrine and nervous systems and emotional states was presented by Seymour Reichlin, M.D., Ph.D. The intent of the article was to illuminate the role of emotional states in disease for clinical medicine. The author discussed the way in which "emotional states or response to stress can modify a person's capacity to cope with infection or cancer and influence the course of autoimmune disease" (p.1246).

In one of the scientific scenarios offered to underscore the relationships, Reichlin reviews the way the nervous system can regulate the immune system. He reports that the neuroendocrine mechanisms of the

hypothalamus direct the anterior pituitary hormones. The hormone's secretion is affected by various stimuli. One of the stimuli is emotional states. Reichlin goes on to state that these hormones can inhibit or stimulate the immune system. For example somatostatin inhibits T-cell proliferation and thyrotropin stimulates IgG synthesis.

Although Reichlin is cautious about the possible implications of emotional states in regards to autoimmune disease, cancer, and infections, he does acknowledge convincingly the relationship between psychological states and somatic events. The author acknowledges the possible causal relationship in disease.

The literature is rich in research underscoring the complex interrelationship between emotional states and the body. For instance, scientists know that the receptors for neuropeptides are located throughout the body (Dienstfrey, 1991; Pert et al, 1985). Neuropeptides are the chemical messengers produced by nerve cells which are critical in the communication between mind and body (Pert, 1991). They have been identified in the gastrointestinal system, the reproductive system and the immune system. In the immune system, a receptor site for a neuropeptide has been located on monocyte (Dienstfrey, 1991; Pert et al, 1985).

The role of the neuropeptide is critical to the proper functioning of the body. The fact that receptors for the messenger of the brain are situated in the limbic system as well as throughout the body underscores the interconnection between mind and body. It gives a physical foundation for why emotion plays a part in the functioning of the immune system. This material manifestation of emotion, as Pert refers to it, can communicate directly to a key component of immunity. As with any chemical messenger, the neuropeptide can influence the action of the entity in which it invades. One of the most interesting aspects of the neuropeptide is that Pert believes that it is "mobilized" by emotion.

This not only a salient point for the psychoneuroimmunology literature, but also for the literature that proposes the theory of the "emergent properties" of the brain.

For the last twenty years, the relationship between psychological states and physiological functioning has been a legitimate scientific endeavor engaged by renowned scientists. However, as legitimate and substantive as the this area is, it really remains in the background. In the public and physical science domains, the psychological component has not been truly accepted despite the breadth and depth of the research. However, this could change, quickly and dramatically. This change could not affect certain scientific disciplines, but also the larger scientific structure.

As dynamic as the content of this scientific investigation is, there is another aspect beyond the content area which is dynamic in its own right. That is the framework in which scientific activity operates. It is important to look at this aspect since it offers insight into the forces at work in science and allows one to understand the inner workings of science. The discussion will be based on Thomas S. Kuhn's (1962) brilliant work entitled, The Structure of Scientific Revolutions. Although there are many views on this topic, it is Kuhn's perspective which is most pertinent.

The discussion will begin with the definition of a paradigm. A paradigm is a "model of investigation that guides the thinking and activities of a community" (Tageson, 1982, p.52). According to Kuhn, paradigms are based on a few major scientific achievements. Throughout history, paradigms have come and gone or been modified. Paradigms of the past that Kuhn cites are Ptolemaic theory that was replaced by the Copernican theory and Newtonian physics being altered by Einstein's relativity theory.

According to Kuhn, a specific paradigm comes to domination when it has proven to be more successful at resolving serious problems than other paradigms. A paradigm that comes to dominate may not always be able to find solutions to all the problems that confront it. However, since the paradigm is more capable of handling problematic issues than a competing paradigm, it is selected to lead the scientific community. Problematic issues that can not be resolved by the paradigm are called anomalies.

Medicine is a scientific endeavor that adheres to the structure of scientific paradigms. It is based on many scientific achievements. In addition, it has been very successful in treating or combating many illnesses. However, although it has lengthened and improved the quality of life, medicine still has many problematic issues still to be resolved. For example, viruses still remain elusive to this scientific community. They are the anomalies in Kuhn's analysis. Given the tools with which they work, viruses are a problematic issue which the medical community is having trouble grasping. At the present time, the major way of combating viruses is to control the symptoms of the disease and not the disease itself (Bloom, 1989).

Anomalies can lead to a few different types of situations. One situation is one in which the specific scientific body can "isolate the anomaly from the community so that the paradigm can continue to operate and there is a minimum effect on the community" (p.41). A second situation is one in which a new paradigm evolves as a result of the paradigm changing in order to problem solve effectively. A third situation is one in which a "scientific revolution" takes place. In this situation, the paradigm that is being used is rendered ineffective and is replaced by one that is more successful than the old paradigm and competing paradigms. However, it is important to recognize that the

scientific revolutions do not take place unless there is a paradigm which can take its place.

With all the developments that are occurring in various disciplines including those in psychology and the many anomalies confronting medicine, one could say that a situation exists that could give rise to paradigm shift or even perhaps a scientific revolution if physics becomes a major player as Candance Pert suggests. To reiterate, a paradigm shift occurs when several discoveries serve to change and expand the existing paradigm in which it is rendered ineffective. This allows a competing paradigm to replace the old paradigm.

The point that is critical is that a competing paradigm must be established before a change occurs. As Kuhn states, a paradigm asserts itself and begins to be recognized when it begins to have specialized journals, a foundation of specialists, societies and maintains a space in the curriculum. This is certainly the case with the "mind/body" paradigm.

There have been numerous journals that have arisen over the past few decades. Psychoneuroendocrinology, Mind/Body Medicine, Advances, Brain Behavior and Immunity are some of the leading journals that are creating a new perspective on health issues. These specialized journals and others such as Health Psychology, Psychosomatic Medicine, and Journal of Psychosomatic Research are underscoring or highlighting the behavioral and psychological aspects of health.

With areas such as psychoneuroimmunology, psychoneuroendocrinology, and many other fields akin to these, there is also a new breed of specialists that are focusing on the psychological modulation of physiological systems. Subsequently, their work is becoming part of curriculums at universities.

These events are solidifying a new paradigm. This paradigm has its own achievements and could possibly have the tools to solve those

anomalies which confronts medicine. Hence, this could be a very important time not only for psychology, but for science, too.

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Appendix A

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Appendix B

Table 24

Predictors for Neutrophils Hypothesis Tests

Study	Statistic(df)	N	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
24.	t = 2.30(18)	20	1989	2	2	2	2	2	1
21.	p = .016	31	1992	1	3	1	1	1	3
27.	t = 1.93(28)	30	1989	3	3	1	1	2	3

Table 25

Predictors for Phagocytotoxic Cells Hypothesis Tests

Study	Statistic(df)	N	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
26.	$\chi^2 = 3.86(1)$	41	1985	1	2	2	2	2	3
26.	F = 11.11(1,21)	23	1985	1	2	2	1	2	1
25.	p < .05	8	1976	2	1	2	2	1	3

Note. P1 = Date of Publication; P2 = Type of Population; P3 = Validity; P4 = Experimental situation; P5 = Type of Treatment; P6 = Duration of Treatment; P7 = Modulation

Table 26

Predictors for Large Granular Lymphocytes Hypothesis Tests

<u>Study</u>	<u>Statistic(df)</u>	<u>N</u>	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
24.	F = 6.58(1,39)	41	1986	1	2	2	2	1	3
5.	F = 19.24(1,21)	23	1991	3	2	1	2	1	1

Table 27

Predictors for Lymphocytes Hypothesis Tests

<u>Study</u>	<u>Statistic(df)</u>	<u>N</u>	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
27.	t = 2.11(28)	30	1989	3	3	1	1	2	3
34.	F = 5.32(1,22)	24	1992	2	3	1	2	1	3
21.	p = .05	31	1992	1	3	1	1	1	1
33.	r = .13(254)	256	1985	2	3	2	1	2	1

Table 28

Predictors for Natural Killer Cells Hypothesis Tests

Study	Statistic(df)	N	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
15.	F = 1.27(1,50)	52	1987	2	3	2	2	2	2
9.	F = 5.59(1,48)	50	1990	1	1	2	2	2	3
9.	F = 7.39(1,61)	63	1990	2	1	2	2	2	3
9.	F = 2.54(1,77)	79	1990	2	1	2	2	2	3
14.	F = 9.87(1,68)	70	1984	1	1	2	2	1	3
17.	F = 4.99(1,41)	43	1992	1	3	1	2	1	1
8.	r = .28(35)	37	1987	2	3	2	2	2	3
2.	F = 7.91(1,21)	23	1990	2	3	2	1	2	1
13.	F = 3.98(1,27)	25	1987	2	2	2	2	2	3
19.	r = -.17(8)	10	1984	1	3	2	2	2	2
23.	r = -.06(8)	10	1989	1	3	2	2	1	2
5.	F = 8.14(1,39)	41	1986	1	2	2	2	1	3
7.	r = -.21(18)	20	1986	1	3	2	2	2	3
23.	r = .14(8)	10	1989	1	3	2	2	1	2
1.	F = 4.99(1,42)	44	1992	1	1	1	2	1	1
30.	F = 16.36(1,20)	22	1994	1	3	1	2	1	1
16.	F = 3.73(1,88)	90	1993	2	3	1	2	1	3
24.	F = 16.95(1,21)	23	1991	3	2	1	2	1	1
29.	p < .05	45	1993	2	1	2	2	1	1
22.	t = 2.32(18)	20	1989	2	2	2	2	2	3

Table 29

Predictors for Immunoglobulin A Hypothesis Tests

Study	Statistic(df)	N	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
14.	F = 6.05(1,42)	44	1984	1	1	2	2	1	1
3.	t = -2.26(8)	10	1985	1	2	1	1	1	1
18.	t = 2.30(8)	10	1986	1	3	2	2	2	3
28.	F = 21.14(1,14)	16	1990	1	2	1	1	2	1
6.	F = 22.46(1,39)	41	1988	3	1	1	1	1	1
10.	F = 23.72(1,28)	30	1988	1	1	2	2	1	3
6.	F = 6.51(1,39)	41	1988	3	1	1	1	1	1
4.	r = .56(10)	12	1993	1	1	1	1	1	1
4.	r = .35(10)	12	1993	1	1	1	2	1	1
20.	t = 3.68(18)	20	1994	1	1	1	2	1	1
31.	F = 6.83(1,28)	30	1987	1	1	2	1	2	1

Table 30

Predictors for Immunoglobulin G Hypothesis Tests

Study	Statistic(df)	N	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
14.	F = 1.43(1,35)	37	1984	1	1	2	2	1	2
32.	t = 2.25(48)	50	1990	2	2	2	2	2	1
6.	F = 20.42(1,39)	41	1988	3	1	1	1	1	1

Table 31

Predictors for Immunoglobuling M Hypothesis Tests

Study	Statistic(df)	N	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
14.	F = 2.61(1,42)	44	1984	1	1	2	2	1	2
6.	F = 4.34(1,39)	41	1988	3	1	1	1	1	1

Table 32

Predictors for B Lymphocytes Hypothesis Tests

Study	Statistic(df)	N	P1	<u>Predictors</u>						
				P2	P3	P4	P5	P6	P7	
17.	F = 4.16(1,40)	42	1984	1	1	2	2	1	3	
22.	t = 2.43(18)	20	1989	2	2	2	2	2	3	
1.	p = .50	44	1992	1	1	1	2	1	2	
24.	p = .50	23	1991	3	2	1	2	1	2	
22.	t = 2.36(18)	20	1989	2	2	2	2	2	3	

Table 33

Predictors for Total T Lymphocytes Hypothesis Tests

Study	Statistic(df)	N	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
13.	F = 4.08(1,31)	33	1987	2	2	2	2	2	3
2.	F = 5.86(1,21)	23	1990	2	3	2	1	2	1
1.	p = .50	44	1992	1	1	1	2	1	2
16.	F = 9.80(1,88)	90	1993	2	3	1	2	1	1
11.	F = 6.17(1,88)	26	1991	2	3	2	2	2	3
24.	p = .50	22	1991	3	2	1	2	1	2
29.	p < .05	45	1993	2	1	2	2	1	1
15.	F = 4.87(1,62)	64	1987	2	3	2	2	2	3

Table 34

Predictors for Helper/Inducer Lymphocytes Hypothesis Tests

Study	Statistic(df)	N	<u>Predictors</u>						
			P1	P2	P3	P4	P5	P6	P7
1.	p = .50	44	1992	3	2	1	2	1	2
16.	F = 6.40(1,88)	90	1993	2	3	1	2	1	1
24.	p = .50	23	1991	3	2	1	2	1	2
29.	p < .05	45	1993	2	1	2	2	1	1
15.	F = 18.49(1,62)	64	1987	2	3	2	2	2	3

Table 35

Predictors for Suppressor/Cytotoxic Lymphocytes Hypothesis Tests

		<u>Predictors</u>							
<u>Study</u>	<u>Statistic(df)</u>	<u>N</u>	<u>P1</u>	<u>P2</u>	<u>P3</u>	<u>P4</u>	<u>P5</u>	<u>P6</u>	<u>P7</u>
15.	F = 1.12(1,62)	64	1987	2	3	2	2	2	2
27.	F = 1.07(1,31)	33	1987	2	2	2	2	2	2
1.	p = .50	44	1992	1	1	1	2	1	1
30.	F = 4.98(1,18)	20	1994	1	3	1	2	1	1
11.	F = 10.25(1,17)	19	1991	2	3	2	2	2	3
24.	F = 4.83(1,20)	22	1991	3	2	1	2	1	1
29.	p < .05	45	1993	2	1	2	2	1	1
16.	F = 39.67(1,43)	45	1993	2	3	1	2	1	3
22.	t = 2.75(18)	20	1989	2	2	2	2	2	3

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