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The effects of perceived control and stress response on immune function following traumatic injury

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THE EFFECTS OF PERCEIVED CONTROL AND STRESS RESPONSE ON IMMUNE FUNCTION FOLLOWING TRAUMATIC INJURY

by

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DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF NURSING SCIENCE

in the

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of the

UNIVERSITY OF CALIFORNIA

San Francisco

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Date **University Librarian**

Degree Conferred: . . . . . .

DEDICATION

Dedicated in loving memory to

my father,

William J. Schrader Jr.

He didn't always understand what I was doing,
but he always believed I could.

ACKNOWLEDGMENTS

There are many individual that provided me with the support needed to accomplish this enormous task. I would like to take this opportunity to thank each one personally. First, I would like to thank the wonderful members of my committee. Dr. Susan Janson, who served as committee chair, proved an invaluable source of knowledge and support. Her review and critique of my numerous drafts was immensely helpful in crafting the final version of this dissertation. Dr. Margaret Wallhagen proved to be invaluable in her knowledge and grasp of the difficult stress and perceived control concepts involved in this dissertation. She helped me make sense of an tremendous amount of information and place it in an understandable context. An especially heartfelt thanks goes out to Dr. Jan Horn, who welcomed me into his very busy lab and provided me with endless hours of his time and energy. His enthusiasm for this project kept me going when I felt like quitting and his demand for excellence forced me to give my very best. This dissertation would never have come to fruition without Dr. Horn's amazing knowledge of trauma and

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ABSTRACT
The Effects of Perceived Control and Stress Response on Immune Function Following Traumatic Injury

Kathleen A. Schrader

Traumatic injury poses a significant psychological and physiological threat, challenging a victim's perceptions of control over their environment and life outcomes. The multiple stressors presented by traumatic injury and hospitalization diminish the patient's perceptions of control, resulting in an increase in subjective stress response. Increase physiologic stress response following traumatic injury has been associated with altered immune function and decreased immunity. The purpose of this study was to investigate the effect of perceived control and subjective and physiological stress response on immune response following traumatic injury.

A prospective, repeated measures design was used to study moderately injured (ISS 9-34) trauma patients (N=10) at 48 and 96 hours post injury. Measures of perceived control (Wallhagen's Current Experience of Situation Subscale); subjective stress (Stress/Arousal CheckList-

SACL); physiologic stress (serum cortisol) and immune responsiveness (mean fluorescence of cell surface receptors, CD 14 on monocytes and CD 25 on lymphocytes) were determined at each data collection point. Normative immune cell response data was also obtained from nine normal volunteers.

Mean (± SD) subjective stress (SACL) was elevated at both 48 (4.1, ± 2.4) and 96 hours post injury (4.6, ± 3.2) above the published normative value (1.7, ± 2.0). Perceived control (range 13-52) demonstrated sample means at 48 hours (40.7, ± 7.8) and 96 hours post injury (39.9, ± 8.9). Decreased perceived control was correlated with increased subjective stress (SACL) and decreased immune responsiveness. Increased perceived control positively correlated with increased immune responsiveness. The sample's mean serum cortisol was elevated above the normal range (5.0-13 µg/dL) at both 48 hours (20.6, ± 8.9) and 96 hours (16.0, ± 5.3) post injury, but failed to correlate significantly with any of the other study variables.

Results indicate that traumatic injury in moderately injured subjects is related to an increase in psychological and physiological stress response. Decreased perceived

control was related to increased subjective stress response and decreased immune responsiveness post injury. Increased perceived control was related to increased post injury immune responsiveness.

Kathleen A. Schaddelee 8/29/95

Doctoral Candidate Date

Susan Janson 8/29/95

Dissertation Chairperson Date

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CHAPTER I

THE STUDY PROBLEM

Introduction and Background

Traumatic injury poses a significant psychological and physiological threat to a patient. To survive the patient must face both the physiologic and psychological challenges it presents. The experience of trauma calls into question the patient's fundamental beliefs about a just and benevolent world and challenges long-held, cherished assumptions about their place in that world (Janoff-Bulman, 1992). The patient's sense of control over the events surrounding the injury and subsequent hospitalization is rapidly eroded by the medical technology that takes charge of his/her body and life. During this time of increased stress and fear, patients are routinely denied access to their loved ones, are subjected to painful procedures, deprived of sleep and are prohibited from performing even the most fundamental activities of daily living. While many of these restrictions and interventions are an unpleasant, but necessary part of the treatment plan, they serve to decrease the patient's sense of control and

increase the stress response experienced. Increased stress response has been associated with altered immune function and diminished immunity following traumatic injury, an outcome with potentially negative consequences.

Nursing care may have an affect on the relationship between stress and immunity following traumatic injury by increasing the patient's sense of perceived control, a demonstrated intervening variable in the stress and immunity relationship (Weisse, 1990; Wiedenfeld et al, 1990 and Cruse, 1992). Nursing interventions that allow patients greater access to their family; provide greater pain control and comfort; and allow patients to actively participate in the planning and administration of their care (Hoffman et al, 1978; Chang, 1978; Moch, 1988; Roberts et al, 1990; Smith et al, 1994) may increase the patient's perceptions of control. However, before interventions to increase perceived control can be tested, the relationships between perceived control, stress response and immunity following traumatic injury, must first be explored.

Statement of the Problem

Investigators have documented the neuroendocrine and immunologic changes that occur following traumatic injury, but little is known about the potential influence of psychological variables on the trauma patient's physiologic status. The emerging field of psychoneuroimmunology proposes that a variety of psychological variables can have significant affect on physiologic outcomes (Bartrop et al, 1977; Schleifer et al, 1983, 1984; Kiecolt-Glaser et al, 1984a, 1984b). Animal studies suggest a subject's sense of control (perceived control) over a stressor may have powerful mediating affects on the relationship between stress and immunity (Sklar & Anisman, 1979; Vistainer et al, 1982; Laudenslage, 1983; Mormede, 1988). While limited in number, human studies support this hypothesis (Weisse, 1990; Wiedenfeld, 1990). Unfortunately, none of these studies have focused on traumatic injury as a stressor which may affect stress response and immunity. Further investigation of the relationships among perceived control, stress response and immunity following traumatic injury is thus indicated.

The Significance of the Study

More than 68 million traumatic injuries occur each year in the United States, resulting in 150,000 deaths due to accidents, suicides and homicides, with 350,000 persons permanently disabled (National Safety Council, 1984). Trauma remains the leading cause of death in persons under 40 years of age and costs our society between $75 and $100 billion annually in direct and indirect costs, far exceeding the expenditures for any other disease entity (Committee on Trauma Research, 1985). Due to the relatively young age of trauma victims, there is an estimated annual loss of 4.1 million productive years as a result of trauma, as compared to the total annual combined 1.7 million lost years for cancer and 2.1 million lost years for heart disease/stroke (National Safety Council, 1984).

Trauma mortality demonstrates a trimodal distribution, with death typically occurring during three distinct phases in the injury course. During the first few minutes following an injury, death is generally the result of massive head injury and/or severe, irreparable lacerations

to major vessels and the heart. In the second phase of trauma, death occurs primarily as a result of uncompensated blood loss, untreated shock, head injury and/or compromised respiratory function. In the third phase, sepsis and multiple organ failure pose the greatest threat and cause 78% of the non-neurological trauma deaths (Baker et al, 1980). This phase of trauma begins hours after the initial injury and lasts days to weeks post-injury (Trunkey, 1985).

It is during the third phase of trauma that the negative influence of the stress reaction is seen. The cascade of metabolic and neurohormonal changes (stress response) that initially occur as a defensive mechanism to ensure survival of the organism, when prolonged, rapidly becomes a catabolic life-threatening response with broad physiologic consequences. A hypermetabolic, hypoperfused and immunosuppressed state ensues, setting the stage for subsequent sepsis and multiple organ failure. This cascade of events is so deadly that sepsis ranks second as the leading cause of death in trauma patients who survive greater than 7 days, surpassed only by deaths due to head injury (Hoyt, 1989).

The high mortality rate from sepsis seen in the acute stages of trauma mandates further investigation of the post injury immunosuppression phenomenon. While medical research has been conducted on the physiological affect of the stress reaction following trauma and its immunologic consequences, little attention has been paid to the mind-body link that exists between the psychophysiological stress reaction activated by a traumatic injury and it's subsequent immunologic consequences. How this relationship between stress response and immune outcome is altered by the influence of the psychological variable, perceived control, is of particular interest to this researcher.

The Purpose of the Study

The primary purpose of this study was to investigate the effect of perceived control and subjective and physiological stress response on immune response following traumatic injury. The specific aims of this study were to:

- Examine whether significant relationships existed between perceived control, subjective and physiologic stress response, and immune response following traumatic injury.
- Determine whether these relationships change over time at early (48 hours) and late (96 hours) post-injury.

The following research questions were posed to explore the specific aims of the study:

- Do subjects sustaining traumatic injury experience changes in perceived control, subjective and physiologic stress response and immune response between early (48 hours) and late post-injury (96 hours)?

- Is immune response at early post-injury (48 hours), related to subjective stress response; physiologic stress response; and/or perceived control at early post-injury (48 hours)?

- Is immune response at late post-injury (96 hours), related to subjective stress response; physiologic stress response; and/or perceived control at late post-injury (96 hours)?

- Is immune response at late post-injury (96 hours), related to subjective stress response; physiologic stress response; and/or perceived control at early post-injury (48 hours)?

CHAPTER II

THEORETICAL FRAMEWORK, BACKGROUND OF THE STUDY, AND LITERATURE REVIEW

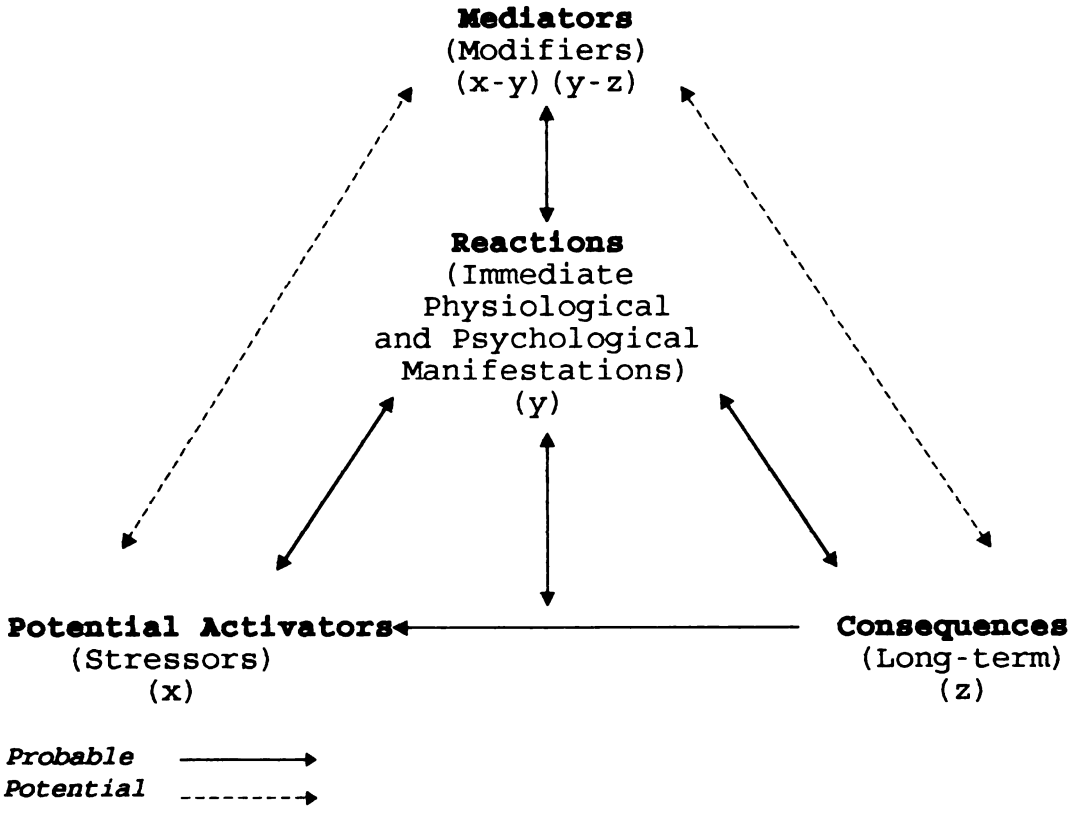
Theoretical Framework

In order to investigate the relationships among perceived control, stress and immune response, the concept of stress must first be placed in a theoretical context which allows closer scrutiny of it's various elements. The conceptual framework proposed by Elliot and Eisdorfer (1982) provides a model for conceptualizing stress within the broader framework of man's interaction with his environment (See Figure 1). It reveals that the effects of the environment on the individual consists of three primary elements; (1) an **activator** or **stressor** in the environment acts to initiate a (2) **reaction** within the individual, (3) resulting in **consequences.**

This activator-reaction-consequences sequence can also be illustrated in an x-y-z formula (See Figure 1). While the elements of this sequence can only be studied in static

isolation (x-y, y-z), in reality this is a dynamic process in which each element in the sequence interacts with the other elements, constantly modifying one another. Each element is further defined by the descriptors or characteristics of its: **organization level** (physiological, psychological, sociological); **intensity** (strength, force, degree); **quantity** (magnitude, amount); and **temporal pattern** (duration, frequency, rate). Consequences also possess an evaluative quality or characteristic which defines an outcome as being either "good" or "bad" or as a negative or positive outcome.

Figure 1. CONCEPTUAL FRAMEWORK FOR STRESS



DESCRIPTORS - Characteristics of Potential Activators, Mediators, Reactions and Consequences:

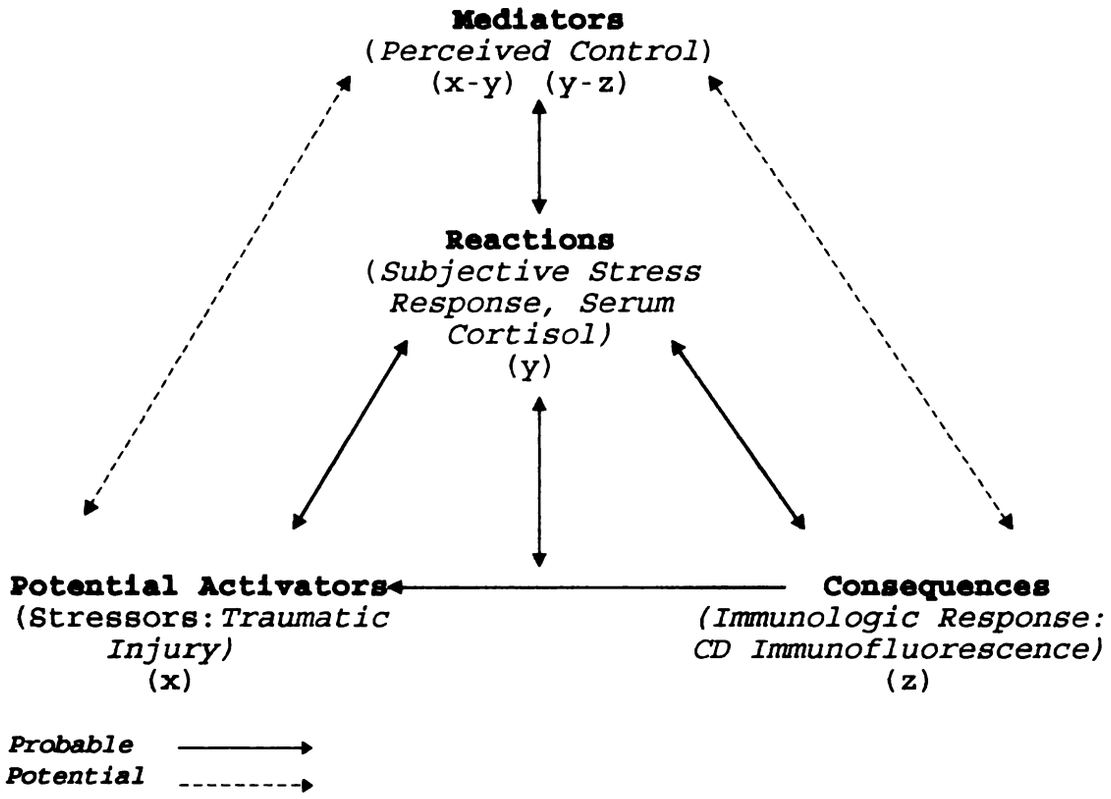
Organizational level -(physiological, psychological, sociological)
Intensity -(strength, force, degree)
Quantity -(magnitude, amount)
Temporal Pattern -(duration, frequency, rate)
Evaluative Quality - Consequences only ("good vs. bad")

NOTE: Adapted from: Elliott, G.R., Eisdorfer, C. (1982) *Stress and Human Health.* New York: Springer Publishing Company, p.19.

Given Elliott's and Eisdorfer's framework for conceptualizing stress, the triad of traumatic injury; perceived control; psychological and physiological stress

response; and immunologic outcomes can be superimposed (See Figure 2).

Figure 2. CONCEPTUAL FRAMEWORK FOR STRESS RESPONSE, PERCEIVED CONTROL AND IMMUNITY FOLLOWING TRAUMATIC INJURY



DESCRIPTORS - Characteristics of Potential Activators, Mediators, Reactions and Consequences:

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Evaluative Quality - Consequences only ("good vs. bad")

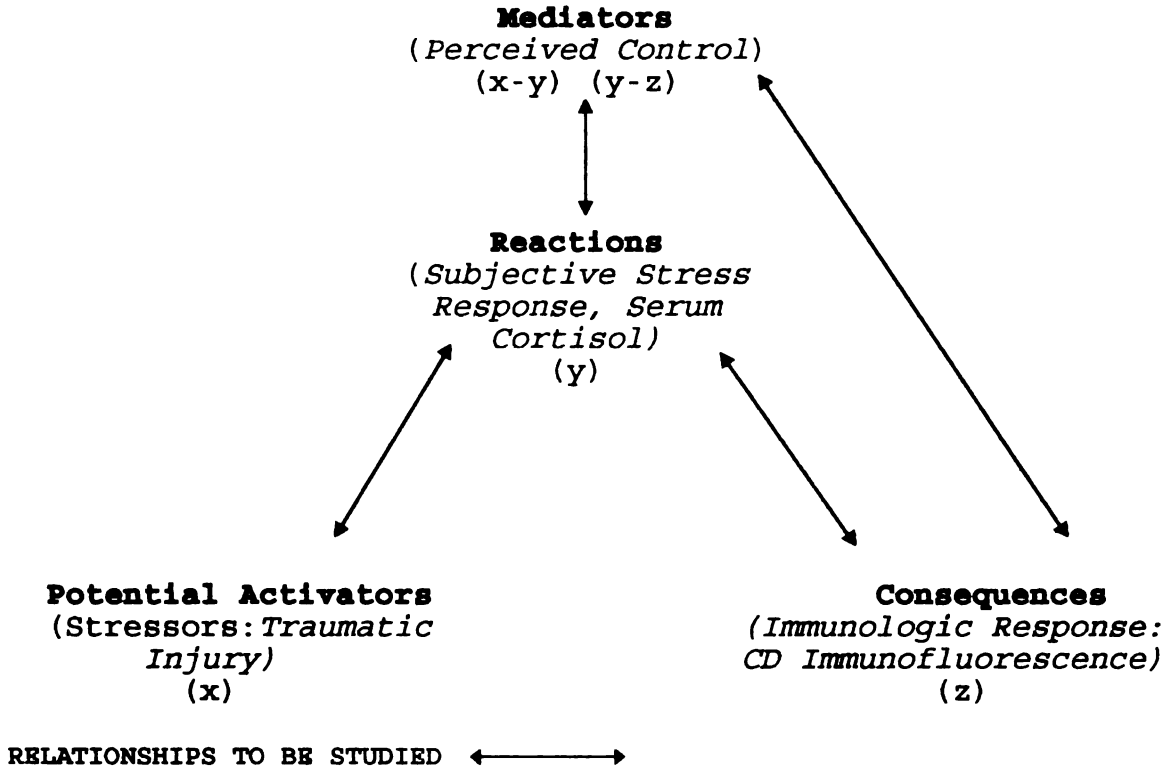
NOTE: Adapted from: Elliott, G.R., Eisdorfer, C. (1982) *Stress and Human Health.* New York: Springer Publishing Company, p.19.

Based on this conceptual framework of stress, perceived control and immunity, the following hypothesis was formulated:

> The patient's current perception of control over his/her injury serves to mediate or intervene in the relationship between stress response and immune function following traumatic injury. The degree of perceived control actualized by the patient determines its mediating affect on stress; with an increased stress response expected in patients demonstrating low levels of perceived control and a decreased stress response anticipated in those expressing high levels of perceived control. These negative correlations will be further related to subjects' immune status, with alterations occurring in the immune responsiveness of cell surface CD antigens.

Figure 3 illustrates the relationships to be studied in this conceptual framework. The nature of these relationships and the underlying, background elements of stress response, immune response, and perceived control will now be explored and placed within the context of the traumatic injury experience.

Figure 3. CONCEPTUAL FRAMEWORK FOR STRESS RESPONSE, PERCEIVED CONTROL AND IMMUNITY FOLLOWING TRAUMATIC INJURY: RELATIONSHIPS TO BE STUDIED.



NOTE: Adapted from: Elliott, G.R., Eisdorfer, C. (1982) *Stress and Human Health.* New York: Springer Publishing Company, p.19.

Background of Stress and Immunity

The importance of psychological stress and it's potential effect on immunity following traumatic injury is substantiated by research results from a wide variety of studies. In recent years a convincing body of knowledge has developed which supports a link between physical and emotional stress and immune responses(Kimsey, 1975,1976; Bartrop et al, 1977; Dorian et al, 1981; Schleifer et al, 1983; Laudenslager et al, 1983; Locke, 1984; Kiecolt-Glaser, 1984a, 1984b; Shavit et al, 1984; Maier et al 1985; Stein et al, 1985; Tonnesen, 1987; Odio et al, 1987; Breier et al, 1987; Mormede et al, 1988; Maier & Laudenslager, 1988; Linn et al, 1988: Kiecolt-Glaser et al, 1988; Kemeny et al, 1989; Weisse et al, 1990; Dobbin et al, 1991; Zachariae et al, 1991; McCarthy et al, 1992; Cruse, 1992; and Evans et al, 1992). Spanning a wide variety of fields including psychology, immunology, neuroscience, and endocrinology this interdisciplinary collaboration has resulted in the growth of a new research discipline, psychoneuroimmunology (PNI). PNI focuses on the elusive

mind-body connection between stress and its immune consequences (Tecoma and Huey, 1985). Solomon (1987) defines psychoneuroimmunology as "complex bi-directional interactions between the CNS (mediating both psychic and biologic processes) and the immune system (not only responsible for resistance to infectious diseases and cancer but also serving newly recognized bio-regulatory functions)".

The theoretical framework of psychoneuroimmunology is based on two general assumptions: 1) all disease/illness is multi-factorial and biopsychosocial in origin and course, occurring as the result of an interaction among a variety of genetic, endocrine, immune, emotional, behavioral and etiologic factors (e.g. bacteria, viruses); and 2) bi-directional communication exists between the nervous and immune systems. These assumptions are supported by an expanding body of evidence which demonstrates that:

- immune responses can be conditioned,
- electrical stimulation of specific brain sites can alter immune response,
- altered immune response and increased tumor susceptibility occurs in experimentally stressed animals,
- activation of the immune system correlates with altered neurophysiological, neurochemical and neuroendocrine function of brain cells (Dunn, 1989).

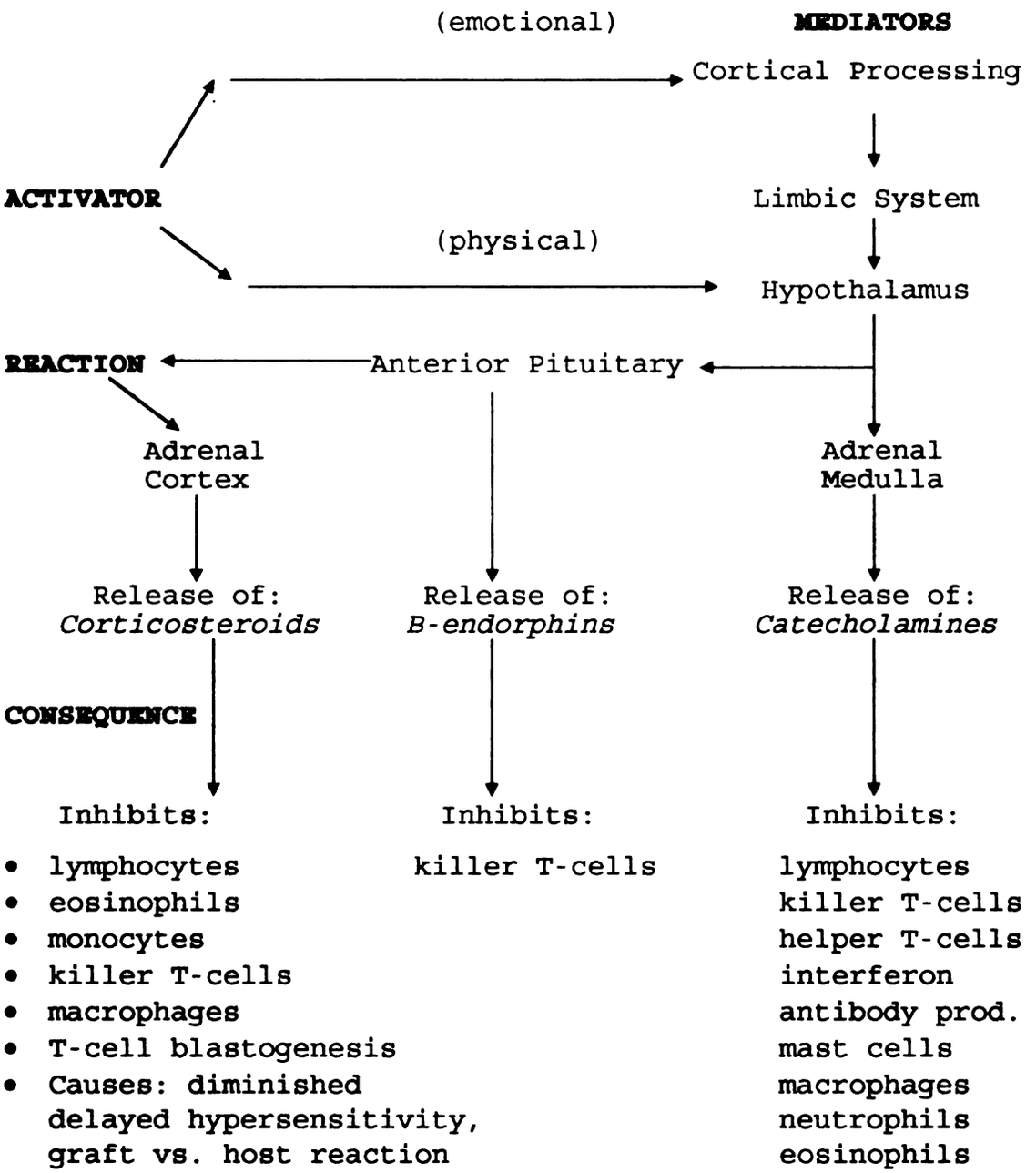
As a result of intensive research efforts, a variety of underlying mechanisms have been proposed to explain the link between stress and immunity. Each theory proposes a different set of biochemical mediators which work to modulate the immune system (immunomodulation). Several proposed theories of immunomodulation include models which emphasize a genetic or developmental basis. Other theories suggest the existence of neuroendocrine-immunoregulatory circuits and/or sensory neurons between the brain and the immune system which allow for direct communication between the two systems (Tecoma and Huey, 1985). The most prominent theory of immunomodulation focuses on the hypothalamic-pituitary-adrenal (HPA) axis (Tecoma and Huey, 1985).

The HPA axis is activated by a wide variety of physical, environmental and psychological activators or stressors, including anxiety, pain, fear, starvation, and physical injury (Axelrod and Reisne, 1984). This activation results in the stimulation of the hypothalamus which acts on the anterior pituitary to cause the release of adrenocorticotropin (ACTH) and several other peptides

(See Figure 4). ACTH in turn, stimulates the release of cortisol from the adrenal cortex and epinephrine and norepinephrine from the adrenal medulla. These neuroendocrine substrates have broad ranging effects on immune cells and their functions as demonstrated in Figure 4. (Borysenko, 1984).

Corticosteroids have been shown to be especially immunosuppressive and are frequently implicated in the stress/immunity relationship (Tecoma and Huey, 1985; Cavagnaro, 1988).

Figure 4. Hypothalamus-Pituitary-Adrenal Axis of Stress and Its Effect on Immune Function.



Note: Adapted from: Borysenko,J. (1984) Stress, coping, and the immune system. In: J.D. Matarazzo, S. Weiss, J.A. Herd, N.E. Miller and S.M. Weiss (Eds.). *Behavioral Health: A Handbook of Health Enhancement and Disease Prevention.* New York: John Wiley and Sons.

Actions of Corticosteroids

Following traumatic injury, an elevation in serum cortisol levels is seen which positively correlates with the severity of injury incurred (Davies et al, 1984; Deitch et al, 1982; Deitch et al, 1984). To understand how elevation in serum cortisol levels affects post injury immune competence a better understanding of the actions of corticosteroids is required.

Cortisol and other exogenous glucocorticoid are reported to have broad immunosuppressive effects (Tecoma and Huey, 1985; Cavagnaro, 1988). Prolonged exposure to sufficient corticosteroids, as seen in stress states, can cause atrophy of lymphoid tissue and destroy lymphocytes (cell lysis) in the thymic cortex in corticosteroid-sensitive animals like the hamster, rat or rabbit.

In man and monkeys, corticosteroids inhibit macrophage and lymphocyte function as well as diminish lymphocyte proliferation (Borysenko, 1984; Munck and Guyre, 1991). These changes in cell numbers and function are thought to be the result of either cell lysis or more likely, cell redistribution to an extravascular compartment (bone

marrow) mediated by a corticosteroid-induced alteration in the cell DNA (Cupps & Fauci, 1982; Calvano, 1986; Cupps, 1989).

It has been hypothesized that the immunosuppressive affects of glucocorticoids occur as the result of two intracellular mechanisms. The first mechanism, increased immune cell intracellular cAMP, is the result of a combination of hormones (cortisol, epinephrine, norepinephrine, prostaglandin, histamine, insulin, somatotropin, endorphins, ADH, and parathyroid) binding to specific cell membrane receptors on the cell membranes of mature leukocytes (lymphocytes, monocytes, and granulocytes). All of these hormones, when bound to the cell membrane receptor sites stimulate the immune cell to generate increased amounts of the second messenger, cyclic adenosine monophosphate (cAMP). The increased levels of cAMP activates intracellular protein kinase, which in turn catalyzes the phosphorylation of regulatory proteins, resulting in inhibition of the cell's genetically encoded enzymatic activity. While elevated cAMP stimulates the proliferation and maturation of immature cells, it inhibits

the function and proliferation of mature, immunocompetent cells (Madden & Livnat, 1991).

A second mechanism of glucocorticoid action on immune cells has been proposed in a model by Munck and Guyre (1991). This model suggests that glucocorticoids freely penetrate the cell membranes of lymphocytes, monocytes and other immune cells to bind reversibly with an unliganded receptor to form a hormone-receptor complex. This hormone-receptor complex becomes activated and rapidly binds with the cell's DNA in the cell nucleus. A change in DNA transcription occurs resulting in an altered mRNA. The resulting altered mRNA is translated into proteins (enzymes, genes, secretory products, etc.) which act as primary effectors of glucocorticoid actions within the targeted receptor cells. In this manner, glucocorticoids can regulate many of the proteins (cytokines, receptors, surface antigens) produced by a variety of immune cells (Munck & Guyre, 1991).

Along with lymphopenia and monocytopenia, other immune cell changes caused by corticosteroids include eosinopenia, granulocytosis, decreased killer T-cell function, T-cell blastogenesis, and inhibited phagocytic cell function

(Calvano, 1986). Clinically, diminished graft-versus-host reaction and decreased delayed hypersensitivity response are typically seen as a result of corticosteroid administration (Calvano, 1986).

While the glucocorticoids secretion seen in stress was originally thought to enhance the body's natural defense mechanism as part of the General Adaptation Syndrome (Selye, 1976), it is now thought that the role of glucocorticoids in stress is to suppress or inhibit normal defense mechanisms (e.g. inflammation) in an attempt to protect the organism from self-inflicted injury (Munck & Guyre, 1986). Thus cortisol secretion may serve to protect the body during periods of stress from autoimmune disease, inflammation and hypersensitivity reactions (Tecoma & Huey, 1985; Munck & Guyre, 1986, 1989).

Cortisol elevation has been documented in a variety of stressful situations. It has been demonstrated in anticipation of surgery (Franksson et al, 1955), depression (Board et al, 1957) and emotional disturbances (Hetzel et al, 1955). Cortisol levels appear to be especially sensitive to stressful situations which involve novelty (Levine & Treiman, 1964; Friedman & Adler, 1967; Friedman

et al, 1967; Basset et al, 1973); uncertainty (Brambella & Penti, 1976; Frankenhaeuser, 1980, 1983, 1986; Rose, 1985); frustration and conflict (Mason, 1968a, 1968b; Henry & Stephens, 1977; Hennessey & Levine, 1979; Frankenhaeuser, 1980; Lungberg, 1980; Ursin, 1980; Borysenko, 1984; Fredrikson et al, 1985) and fear (Calvano, 1986). Because of its high degree of response specificity to certain types of stressors (i.e. novelty, uncertainty, frustration and fear), and its long-term effects, cortisol has consistently been chosen as the measure of choice in studies quantifying stress response (Frankenhaeuser, 1986). These qualities, along with its broad immunosuppressive consequences, makes it an excellent measure of the effects of stress on immunity. Cortisol elevation as a measure of physiologic stress is especially appropriate in the context of traumatic injury, a stressor which incorporates high degrees of uncertainty, fear, novelty and unpredictability.

As mentioned earlier, cortisol has been shown to have board immunosuppressive effects (Tecoma and Huey, 1985; Cavagnaro, 1988). In order to understand the immune changes related to increased cortisol levels, it is first

necessary to understand the various components of cellular immune response and how they are measured.

Cellular Components of Immune Response

The cellular immune system is comprised of eight major lineages of cells: erythroid (erythrocyte); megakaroyocytic (platelet); eosinophilic (eosinophil); basophilic (basophil); myelocytic (neutrophil); monocytic (monocyte/macrophage); B lymphoid (B lymphocyte); and T lymphoid (T lymphocyte). All of the lineages are derived from a common pluripotent stem cell found in the bone marrow (Ogle et al, 1989).

Lymphocytes - Lymphocytes are differentiated from a common lymphoid progenitor cell in either the thymus into T cells (80% of total lymphocytes) or in the bone marrow into B cells (10 - 15% of total lymphocytes). Lymphocytes are constantly recirculating through the blood, lymph and various lymphoid organs (i.e. thymus, spleen, lymph nodes and lymphoid aggregates). There are two major subpopulations of mature T cells: T4 (T-helper and T-suppressor inducer cells), responsible for helper functions and delayed hypersensitivity and T8 (T-cytotoxic and T-

suppressor cells), responsible for cytotoxic and suppressor activity (Ogle, 1989).

Monocytes - The monocyte lineage is also derived from the pluripotent stem cell in the bone marrow differentiating into non-lymphoid and myeloid stem cells. Within 24 hours of their generation monocytes enter the blood stream and migrate to various tissues throughout the body where they further differentiate into resident macrophages. Once established in the various sites they assume morphological and functional characteristics specific to the tissue (e.g. kupffer cells in liver, alveolar macrophages in lungs). Monocytes/macrophages accumulate rapidly at sites of inflammation where they ingest protozoa, bacilli, viruses, antigen-antibody complexes and other inorganic matter reflecting their principal function of host defense via chemotaxis, phagocytosis and bacterial killing . Macrophages also process antigen and present it to the activated T cell, express receptor sites for immunoglobulin binding, and secrete a wide variety of substances including interleukin 1, tumor necrosis factor and prostaglandins (Widmann, 1989; Benjamini and Leskowitz, 1989; Ogle et al, 1989).

Granulocytes - Granulocytes or polymorphonuclear leukocytes are divided into three categories; neutrophils, eosinophils, and basophils and develop from the myeloid stem cell in the bone marrow. Granulocytes are produced in large numbers, represent 60 to 70% of the circulating white blood cells and have a lifespan of 2 to 3 days. Like monocytes, granulocytes are quickly attracted to sites of inflammation and play an important role in cellular defense via their chemotactic, phagocytic, enzyme secretory, oxidative and bactericidal properties (Sigal and Ron, 1994).

Measurement of Immune Response - The techniques used to measure immune response following traumatic injury have mirrored those commonly utilized in other areas of clinical immunology. These traditional approaches include methods which examine delayed hypersensitivity response (Renk et al, 1982), cellular proliferation (Antonacci et al, 1984; Faist et al, 1986; McRitchie et al, 1990), interleukin production (Miller-Graziano, 1988), phagocytosis (Duque et al, 1985; Gadd et al, 1989), cytotoxicity (Alexander et al, 1970; Grogan et al, 1973) and chemotaxis properties (Christeau et al, 1979; Meakins et al, 1978; Dietch et al,

1984; Moore et al, 1986). While these techniques have resulted in valuable information, they frequently require expensive equipment and are often cumbersome and time-consuming to perform (Sigal and Ron, 1994).

More recent studies of immunosuppression following traumatic injury (Calvano et al, 1986; Calvano et al, 1987; Calvano et al, 1988; Babcock et al, 1990; Jackson et al, 1990; Kruger et al, 1991; White-Owen et al, 1992; White-Owen et al, 1993) have utilized the innovative technology of flow cytometry to sort cells by phenotype for specific cell populations (e.g. T-cells, B-cells, monocytes, natural killer cells, etc.), allowing close scrutiny of a large number of cells in a very brief period of time. Utilizing immunofluorescent stains joined to highly specific monoclonal antibodies, these dyes are linked to "cluster determinants" (CD) or antigen receptors on cell membrane surfaces. Numerous CD antigens have been identified and classified, with many of their functional properties defined (e.g. CD25 is found on activated T-cells and acts as a receptor for interleukin 2). Using cell flow cytometry methods the immunofluorescently tagged cells are then passed in front of a series of lasers and, based on

the light refracted, the cell's size and granularity can be identified, thus determining whether it is a lymphocyte, monocyte or neutrophil. Using this method the cell's fluorescent emission can be measured, which correlates with CD antigen surface expression. Upon stimulation, cells demonstrating increased CD immuofluorescence denote enhanced antigen responsiveness, while cells showing decreased CD immunofluorescence are considered to have suppressed antigen responsiveness (Sigal and Ron, 1994).

Given the relative ease and speed of cell phenotyping using flow cytometry methods and the highly specific information it yields, these methods are especially well suited to measuring post-injury immunocompetence in large numbers of subjects.

The Concept of Perceived Control

The psychoneuroimmunology literature suggests that a subject's psychological state can influence his/her physiological status. It further suggests that a subject's perception of control over a stressor can greatly alter the resultant stress and immune responses experienced (Sklar & Anisman, 1979; Visintainer, 1982; Laudenslager et al, 1983;

Maier & Laudenslager, 1988; Mormede et al, 1988; Weisse, 1990; Wiedenfeld et al, 1990; and Cruse, 1992). Traumatic injury poses a significant threat to a victim and greatly taxes his/her perception of control over the situation. Perceived control is a complex and multifaceted construct and a clear understanding of it is required prior to examining its' relationship to stress and immunity.

The drive to control events in our lives is widely acknowledged in the literature (Langer, 1983; Fisher, 1984; Thompson, 1991) and is seen as instrumental in mediating or ameliorating the effects of stress (Glass & Singer, 1972; Johnson & Leventhal, 1974; Langer & Rodin, 1976; Johnson et al, 1978; Miller, 1978; Abramson et al, 1980; Padilla et al, 1981 and Auerbach et al, 1983). As Bandura (1982, p.36) notes; "To the extent to which one can prevent, terminate, or lessen the severity of aversive events, there is little reason to fear them".

The potential benefits of control in regards to health status have been clearly delineated by Wallston (1989) who identifies three postulates for the theoretical linkages between control and the effects of stress:

- "a lack of control can act as a stressor and have a direct, negative effect upon one's health status;
- providing a sense of control to a person experiencing a stressor may buffer the deleterious effects of the stressor;
- a sense of control might increase the likelihood that the individual would engage in one or more health behaviors, thus having a direct, positive effect on his or her health status." (p.85)

Given these postulates it is obvious that influencing the patient's perception of control in a given health care situation can significantly affect his/her ability to cope with stressful medical/nursing interventions; focus patient's efforts on curative processes; and encourage health-enhancing behaviors. The central role control appears to play in mediating the effects of stress underscores the importance of this construct and illustrates the need for further investigation. This need is especially apparent when considering the trauma victim's stress response to injury. The patient is placed in a frightening and foreign hospital environment, experiencing sensations and situations never before encountered. His/her normal mechanisms of coping and obtaining control are seriously challenged. This could result in a diminished sense of perceived control and an even greater physiological and psychological stress response,

potentially initiating an alteration in immune function. For these reasons a better understanding of perceived control and its relationships to stress and immunity are crucial.

Control Paradigm

The construct of control is organized around a reinforcement paradigm which proposes the existence of a relationship between an individual's action and the outcomes or results of that action (i.e. reinforcements). The paradigm further proposes that over a period of time, the individual begins to develop generalized expectations about the frequency of occurrences of reinforcements contingent upon his/her action (McLaughlin, 1971). This reinforcement paradigm has provided the theoretical basis for Rotter's Social Learning Theory (1954), which have served as a major foundation for the conceptualization of the control construct in current literature.

Rotter's Social Learning Theory proposes that individuals form general and specific expectancies about the determinants or causations of their reinforcements based on prior experiences and learning. The individual

develops a belief of the self as causing or not causing the outcomes that follows their behavior. They view these outcomes, in varying degrees, as caused by either their own behavior (i.e. perceived control) or due to events/forces outside themselves or their control (Rotter, 1954).

Definitions of Perceived Control

A consistent problem in conceptualizing and measuring perceived control is the lack of a definitive definition for this elusive and highly subjective construct. Various definitions and typologies of control have been offered, and while there are many differences, certain elements consistently appear.

Central themes extracted from the literature suggest that control must be viewed as a cognitive process in response to a stressful stimuli, which provides the individual with a perception of some element of choice and an ability to affect change either in the environment, situation or oneself to achieve a desirable and valued consequence. Based on this assessment the most global and encompassing definition of perceived control, is the one offered by Wallston (1987, p.5); "the belief that one can

determine one's own internal states and behavior, influence one's environment, and/or bring about desired outcomes."

As Rodin (1979) defines it, perceived control is the expectation that one has the power to make choices which will obtain desired outcomes. Along with a sense of freedom of choice, it also involves a belief in a causal link between one's actions and outcomes. The crucial element in perceived control is the assumption (which varies in conviction according to individual and situation) that one's actions are responsible for the outcomes that occur.

Primary Vs. Secondary Perceived Control

While the uncontrollability theorists (helplessness and locus of control researchers) interpret the passivity and withdrawal (inward behavior) demonstrated by subjects in uncontrollable stressful situations as signs of relinquished perceived control, Rothbaum, Weisz and Snyder (1982) conceptualize these apparent attributions of uncontrollability as another type of perceived control, i.e. "secondary control". According to Rothbaum et al (1982) primary perceived control is obtained by attempting

to bring the environment or situation into line with one's wishes, while secondary control involves bringing oneself and one's expectation in line with the environment or situation. Rothbaum et al (1982) contends that secondary control comes into play when subjects employ attributions such as illusionary control (e.g. luck) and vicarious control (e.g. submission to a powerful other - God). Interpretive control is used by subjects in these situations to derive meaning from otherwise uncontrollable events in an attempt to control them. Inward behaviors of passivity and withdrawal are thus conceptualized as behavioral reflections of this form of secondary control, reflecting the subject's attempts to come into line with the reality of a given situation rather than change it.

Traumatic injury provides a unique and overwhelming threat to the trauma victim. Perceptions of control, especially primary control, are quickly altered leaving the victim to doubt his/her ability to "influence one's environment, and/or bring about desired outcomes (Wallston; 1987, p.5)." Just when the trauma victim most needs to believe in his/her ability to control events, the traumatic injury experience demonstrates just how little control one

actually has over life. The concept of secondary control may be crucial at this point. Deprived of the ability to exercise primary control over events, a trauma victim may rely heavily on secondary control as a means to attain a perception of control over the stressful experiences. The victim may seek to "come in line" with the current situation and passively rely on health professionals to provide care and the necessities of life. The trauma victim may also surrender control to a higher power, such as God, fate or luck. For some victims these passive roles may be sufficient to attain a sense of control, while for others it may provide an additional source of stress, further increasing the stress response.

The Relationships Between Stress, Control and Immunity

Review of the Literature

STRESSORS

Psychological Stressors

While the psychological implications of traumatic injury and its affect on immunity have not yet been explored, human studies in psychoneuroimmunology have focused on a variety of stressful psychological stimuli and their relationships to immunity. These stimuli include chronic, long-term, psychological, life stressors such as, spousal bereavement (Bartrop et al, 1977); depression (Schleifer et al, 1983, 1984); and loneliness (Kiecolt-Glaser et al, 1984a, 1984b).

Bereavement has long been implicated as the underlying cause for illness and death in surviving family members after the loss of a loved one (Schmale, 1958; LeShan, 1959; Solomon et al, 1974) and its relation to immunity has been explored by several researchers (Bartrop et al, 1977; Schleifer et al, 1983). Both Bartrop et al (1977) and

Schleifer et al (1983) demonstrated a lowered T-lymphocyte proliferation response to mitogen stimulants in subjects who were experiencing spousal bereavement.

Clinical depression has also been associated with a decrease in immunity. Lower lymphocyte responses to PHA, Con A and pokeweed mitogen (PWM) were reported in depressed patients when compared with non-depressed psychiatric patients and normal subjects (Kronfol et al, 1983; Schleifer et al, 1984, 1985).

Mood has been implicated as a stressor which alters immunity. A study by Kemeny et al (1989) examined the relationships among stressful life experience (acute and chronic), negative mood, decreased helper-inducer (CD4+) and suppressor-cytotoxic (CD8+) T cells, and the increased reoccurrence of genital herpes simplex. Loneliness and the absence of supportive interpersonal relationships have also been suggested as powerful stressors linked to suppression of the immune response (Kiecolt-Glaser et al, 1984a, 1984b; Kiecolt-Glaser et al, 1988).

Experimental Simulated Models of Stress

Short-term experimentally induced stress has also been used to study the affects of various stressors on immunity. Under experimentally controlled conditions 12 young women (21-41 years) and 11 elderly women (65-85) were asked to complete a brief (12 minute), stressful mental arithmetic exam (Naliboff et al, 1991). Both groups demonstrated an increase in epinephrine levels, cardiovascular parameters (heart rate and blood pressure), subjective stress, anger, and anxiety. These changes were accompanied by an increase in the numbers of CD-8 suppressor/cytotoxic T cells and natural killer (NK) cells. While the younger group also demonstrated an increase in NK activity (killing of target cells), the older women failed to show a stress-related increase in NK activity. No change in helper/inducer T cells, total T cells or B cells was seen following the stressor in either group. The absence of NK activity in the older women led researchers to conclude that NK cell mobilization and NK activity may show a differential response to stress. They also suggested the possibility of an age-related deficit in the regulation of NK activity under stressful conditions.

In a study of hypnotically induced emotions, twenty healthy male and female subjects were made to recall and relive maximally, disturbing, negative and maximally, pleasurable, positive emotional experiences while under hypnosis (Knapp et al, 1992). Negative emotions (sad, angry, anxious) were associated with significant declines in lymphocyte response to three proven T and B cell stimulants; phytohemagglutinin (PHA), concanavalin A (Con A) and pokeweed mitiogen (PWM) (Sigal and Ron, 1994) . These changes were followed by a return to baseline pre-emotion levels. There was a similar, but less significant trend in immune functions following positive emotions. A slight increase in NK cell activity was also noted in relation to negative emotions. These results differ from those of Naliboff et al (1991), leading the researchers to suggest that observed difference might be due to differences in study designs or in the emotional responses evoked. Of special interest were the decreased immune levels seen following positive emotions which researchers suggested may have been the result of an experimental design which evoked general feelings of anxiety and

excitement in all subjects regardless of the emotions experimentally elicited.

A significant increase in NK cells and T-suppressor cytotoxic cells was demonstrated when fifty male subjects were placed in a potentially, uncontrollable, stressful situation (Brosschot et al, 1992). Subjects were asked to solve a difficult puzzle and then to explain their solution to "another subject" who was actually a member of the research team. It was prearranged that neither the puzzle solving nor the solution explanation would be successful, resulting in subject frustration. When compared to a control group, the experimental group demonstrated mild psychological stress, a significant increase in NK cell which returned to baseline within 15 minutes and an increase in T-helper/cytotoxic cells. Lymphocyte counts were increased and were explained by the authors as a result of the redistribution of lymphocytes into peripheral blood, secondary to epinephrine's influence on lymphoid organs (Crary, 1983). A slight decrease in T-helper/suppressor ratio was also noted and thought to be due to the increase number of circulating cells.

Traumatic Injury as a Physiologic Stressor

The fact that immune suppression occurs following a traumatic injury is well established in the current literature (Howard, 1979; Miller et al, 1982; Renk et al, 1982; Faist et al, 1986; Calvano et al, 1986, 1987, 1988; Miller-Graziano et al, 1988; McRitchie et al, 1990) and it is generally accepted that the increased risk of infection seen post-injury is related to this decrease in host resistance (Calvano, 1986). Studies have demonstrated a direct correlation between the severity of injury and the magnitude of alteration in lymphocyte, neutrophil and reticuloendothelial function (Davis et al, 1984; Dietch et al, 1982; Dietch et al, 1984).

While recent findings support a causal relationship between trauma and immunosuppression, controversy still exists as to its underlying mechanisms. Proposed hypotheses have focused on the release of trauma-induced immunosuppressive factors which directly or indirectly down-regulate the normal immune response (McLoughlin et al, 1979; Christou and Meakins, 1979). Hypothesized factors include the low molecular weight peptide SAP (Ozkan et al, 1989); prostaglandin E2 (Ninnemann et al, 1983);

interleukin-1 (Clowes et al, 1985); tumor necrosis factor and cachectin (Beutler et al 1985); endotoxin (Deitch and Berg, 1987); Beta endorphins (Levy et al, 1986); depletion of fibronectin (Scovill et al 1977) and elevation in stress hormones (Deitch and Bridges, 1987).

Stress Hormones and Traumatic Injury - Changes in stress hormone levels following trauma have been well documented in the literature (Carey et al, 1971; Meguid et al, 1978; Barton et al 1987; Amaral et al, 1988; Calvano et al, 1986, 1987, 1988; Jeffries et al, 1992) and include: an increase in corticosteroids, catecholamines and growth hormone; and a decrease in thyronines and insulin (Calvano, 1986). Like stress researchers, who propose that hormonal increases induced by emotional and physical stress are related to immunosuppression; investigators in trauma also suggest that the hormonal changes seen after the physiologic stress of trauma are related to post-injury immunosuppression (Deitch, 1987; Renk et al, 1982; Calvano et al, 1986, 1987, 1988).

Calvano (1986) proposes that hormones, and perhaps all other immunosuppressive factors, exact their affects on the immune response via a common pathway, the cyclic AMP of the

lymphoid-cell. As described earlier, increases in the level of cyclic AMP in lymphoid-cells results in the inhibition of activity of the immune system. The changes seen in hormone levels following traumatic injury, their affect on cyclic AMP and their immune consequences are summarized in Table 1.

Table 1. Trauma-induced Hormonal Changes and Their Influence on Cyclic AMP and Immune Responsiveness.

HORMONE	CHANGE INDUCED BY INJURY	EFFECT ON CYCLIC AMP	EFFECT ON IMMUNE RESPONSE
Cortico-steroids	Increased	Increased	Decreased
Catechol-amines	Increased	Increased	Decreased
Thyronines	Decreased	Decreased	Decreased
Insulin	Insulin Resistance	Increased	Decreased
Growth Hormone	Increased	Unknown	Increased

Note. Hormonal mediation of immune dysfunction following thermal and traumatic injury. Calvano, S.E., 1986, In Gallin J.I. and Fauci, A.(Eds.)*Advances in Host Defense Mechanisms*. Raven Press: New York.

Cortisol Secretion and Traumatic Injury - An elevation in serum cortisol levels is seen immediately following a

traumatic injury in both animals (Amaral et al, 1988) and humans (Hume et al, 1956; Meguid et al, 1974; Stoner et al, 1979; Vaughan et al, 1982; Frayn et al, 1983; Barton et al, 1987; Woolf, 1992). Studies conducted by Stoner et al (1979) and Barton et al (1987) demonstrate that at 2 hours post-injury this increase in serum cortisol is positively correlated with the severity of injury in subjects sustaining minor to moderate injuries (Injury Severity Score of 1-12, see page 94 for explanation of Injury Severity Score scale) (Stoner et al, 1979). At high levels of injury severity (ISS >13) serum cortisol levels demonstrate a negative correlation (Stoner et al, 1979; Barton et al, 1987). This decrease in serum cortisol related to severe injury may be due to a failure of the adrenal cortex to respond normally, secondary to diminished blood flow to the cortex (Barton et al, 1987).

Over time the relationship between serum cortisol and injury severity changes. At later sample intervals (2.1 - 12 hours post-injury) minor and moderate injuries demonstrate a stronger positive correlation with ISS, while the negative correlation between serum cortisol and severe

injury disappears as serum cortisol levels increase along with injury severity (Barton et al, 1987).

The findings suggesting an overall increase in serum cortisol levels among critically injured patients are supported by Calvano et al (1993) who reports a cortisol increase of more than two fold (48.4 µg/dL) over baseline at 24-48 hours post critical burn injury (burn = 30-44% total body surface area). These findings were identical to increased cortisol levels demonstrated after administration of endotoxin and cortisol infusions to healthy control subjects (Calvano et al, 1993). Similar results are reported by Jeffries and Vance (1992) who identified a sustained plasma cortisol range of 456.6 nmol/L (± 78.4) to 684.2 nmol/L (± 93.5), (normal range, 138 to 497 nmol/L) in six trauma patients during days 1 to 13 post burn injury (burn = 15-45% total body surface area) (Jeffries and Vance, 1992). These findings suggest that while initial serum cortisol levels may be decreased in severely injured patients during the early hours post-injury, cortisol levels demonstrate a positive correlation with injury severity in later phases of the post-injury period.

Traumatic Injury, Cortisol Increase and Cellular Immune Changes - The immune changes seen after trauma are due at least in part, to the affect of cortisol on various immune cells and functions. Pharmacological doses of corticosteroids have been shown to produce rapid lymphopenia, monocytopenia, eosinopenia and granulocytosis in normal subjects and animal models (Dougherty and White, 1944). They also have been demonstrated to cause thymic involution; depressed cell-mediated immune response via a decrease of T-killer and natural-killer function; decreased mixed lymphocyte responsiveness; diminished T-cell blastogensis; inhibited phagocytic cell functions; diminished delayed hypersensitivity and changes in humoral (B-cells) immunity (Calvano, 1986).

The immune changes seen following the physiological stress of an injury are similar to those seen after administration of pharmacological doses of corticosteroids to normal human subjects (Antonacci et al, 1982; 1983). A profound lymphopenia occurs without an overall reduction in the total number of lymphocytes. Only T cells (T4) with helper/inducer function are affected, while suppressor/cytotoxic T cells (T8) remain constant or

decrease only slightly (Cupps et al, 1984). Whether this change in humans is due to sequestering of the T cells in the bone marrow is unclear, but studies of injury in rat models reveals a significant increase in helper/inducer T cells in the bone marrow two days after injury (Calvano, 1984).

Corticosteroids also have a direct suppressive affect on lymphoid cell activity, which appears to affect T cells more strongly than B cells. This affect on T cell proliferation appears to be due to inhibition of interleukin-2 which mediates T cell growth. In a study of burn patients who demonstrated decreased lymphocyte proliferation, interleukin-2, but not interleukin-1 was found to be significantly reduced in cell cultures (Wood et al, 1984).

Following burn trauma, phagocytic cell functions are significantly decreased with intracellular killing and chemotaxis most affected and phagocytosis least affected (Grogan, 1976). While a transient monocytopenia is seen, the opposite occurs for blood granulocytes with a substantial neutrophilia being seen. Whether this increase is due solely to the direct affect of corticosteroids or is

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the result of catecholamine influences on the granulocytes is unclear (Calvano, 1986).

A series of studies conducted by Calvano and associates highlights the immune changes related to the increase in serum cortisol seen following traumatic injury (Antonacci et al, 1984; Calvano et al 1986, 1987, 1988). Antonacci and associates (1984) in a study of 30 burn patients (22 men and 8 women) with a mean body surface area (BSA) of 44% noted a marked decrease in the number and percentage of T cells and CD 4 within 48 hours post burn injury. No change was seen in CD 8, while monocyte numbers increased in the first 48 hours. These results correlated with a mean increase in serum cortisol.

Similar results are reported by Calvano (1986, 1987) in a study of 114 burn patients with a burn injury of 42% mean BSA compared to 13 healthy volunteers given epinephrine and cortisol infusions for six hours. The percentage of CD 4 and CD 3 subsets were equally decreased in both the burn injured group (48 hours post burn) and the cortisol infusion group (after 6 hour infusion), while serum cortisol levels were elevated. Significant decrease

in lymphocyte proliferation was also demonstrated in these groups. No change was seen in the immune variables of the epinephrine infusion group.

Calvano et al (1988) demonstrated similar results in a study of 10 burn patients with a mean BSA 51%. While serum cortisol was not measured in this study, a decrease in CD 3 and suppressor CD 4 percentages was seen along with a decrease in total number of lymphocytes. Helper CD 4 and CD 8 remained unchanged.

The studies just discussed clearly demonstrate the immune changes that occur after a traumatic injury and their close correlation with serum cortisol. These results suggest that the increase in serum cortisol seen after traumatic injury may be related to the subsequent changes seen in lymphocyte populations.

MEDIATING VARIABLES

Animal Studies

The increased experimental control inherent in animal models allows for identification of design and subject variables which can modulate the affects of stress on immunity. Mediating variables which have been identified

and explored in animal models include: timing of stressor introduction and immediacy of the response measurement; chronicity and intensity of the stressor; predictability and controllability of the stressor; and variables inherent to the subject such as age and sex (Keller et al, 1991).

Timing of Stressor and Response Measurement - While stress in animal studies has generally resulted in immunosuppressive outcomes, protective effects have been noted and are often the result of variations in study design and/or implementation. Timing of the introduction of the stressor and immune measurement are extremely important. For example, mice show a distinct bi-phasic immune response when exposed to noise. An initial immunosuppression is seen during the first two weeks of exposure, followed by a pronounced overshoot in lymphocyte cytotoxicity and proliferation (Monjan & Collector, 1977; Borysenko, 1984). These seemingly contradictory findings lend support to the proposal that while acute stress may be associated with immunosuppression, habituation and a return to normal or increased immune levels may occur in situations of chronic stress (Keller et al, 1991). Given this tendency toward habituation, the importance of timing

the stressor relative to the response measurement is underscored.

Chronicity and Intensity of the Stressor - Another explanation for these contradictory findings may be inherent in the stressor itself. Chronicity and intensity of the stressor appear to be crucial determinants of its impact. It is apparent that a stressor must be of sufficient intensity and duration to be perceived by the subject as stressful, thereby evoking an immune response. It has been suggested that stressors which fail to demonstrate immunosuppression may lack sufficient intensity and/or chronicity to initiate a stress reaction in the subject (Adler, 1983). An example of this phenomenon is seen in the study conducted by McCarthy et al (1990) in which rats were exposed to short-term (24 hour), high intensity noise stress (80 decibels of rock music). Oxidative burst and interleukin-1 production were reduced in neutrophil and macrophage populations, but contrary to previous findings (Monjan & Collector, 1977) lymphocyte function was not impaired. These findings led the researchers to suggest that insufficient intensity and duration of the noise stressor may have been the reason for

the differing results and could have posed as significant confounding variables in their study design (McCarthy et al, 1990).

The importance of stressor intensity is also emphasized in a study of cellular immune response in rats by Keller et al (1981) using a series of graded tail shocks to measure the affect of stress on PHA stimulated lymphocyte proliferation and absolute number of circulating lymphocytes. Results reveal that progressively graded stressors produced increasingly greater lymphocytopenia and suppression of lymphocyte proliferation. These findings support the conclusion that stress suppresses cellular immune response proportional to the intensity of the stressor (Keller et al, 1981).

Subject Variables - A variety of variables inherent to non-human subjects have been identified that affect stress response in animal models. Extensive studies have been conducted on how animals react to various stressors (e.g. crowding vs. isolation; escapable vs. inescapable shock), with findings that appear to be dependent on the species and strain of animal (Rabin & Salvin, 1987), age (Odio et al, 1987), sex of the subject (Ackerman et al, 1988) and

psychological variables, such as isolation (Laudenslager et al, 1982; Jessop et al, 1987) and controllability (Sklar & Anisman, 1979; Visintainer et al 1982; Laudenslager, 1983; Mormede, 1988).

Sex and Species Strain - Rabin & Salvin (1987) found that while there was an initial, marked suppression in splenic lymphocyte responses to Con A, T-helper cell deficit and decreased interleukin 2 production following crowded housing conditions of C3H/HeJ male mice, no such change was seen in female C3h/HeJ mice or male/female C57BL/6J mice under similar conditions. These findings led researchers to suggest that sex and certain species strain act to mediate the relationship between stress and immune function in animal studies.

Age - Age has been implicated as a factor in the stress and immunity relationship in both animal (Odio et al, 1987) and human studies (Schleifer et al, 1989). Splenic lymphocyte response to Con A and LPS (lipopoysaccharide endotoxin) was suppressed in 12 and 18 month old male Fisher 344 rats following shuttle box and escapable footshock stress, but not in 25 month old rats (Odio et al, 1987). The etiology of this age-related

difference is unclear, but may be due to an age-induced alteration in either the subject's physiologic response to stress and/or immunity.

Isolation - Animal studies have also provided insight into the potential influence of psychological variables on the stress/immunity relationship. Rabin and Salvin (1987) in their study of housing of mice note that isolation of mice induces immunoenhancement. This contention is supported by Jessop et al (1987) in their study on the affects of isolation of Sprague-Dawley rats following two weeks of group housing. While isolation has been associated with immunoenhancement in mice and rats, similar findings have not been found in primates (Laudenslager et al, 1982) or humans who demonstrate immunosuppression when socially isolated (Kiecolt-Glaser et al, 1984b).

The immune affects of maternal separation and isolation were studied in a group of infant monkeys by Laudenslager et al (1982), after it was observed that infant primates demonstrate increased vulnerability to illness during periods of maternal separation and loss. Lymphocyte proliferation in mother and infant bonnet monkeys was observed during a 14 day separation, with

infant monkeys demonstrating a suppression of lymphocyte proliferation compared to their pre-separation baseline findings. While T cell response to Con A and PHA mitogens were depressed, B cell responsiveness to pokeweed mitogen was not significantly affected and was thought to be due to the immaturity of the infant monkeys' humoral immune system.

Following reunion of infants with their mothers, normal immune responsiveness was restored. The maternal monkeys demonstrated similar findings, both during the separation and upon reunion. The results lend support to the hypothesis that stress induced immunosuppression underlies the observed increased vulnerability of primates to illness during periods of social isolation (Laudenslager et al, 1982).

Controllability - In an animal model illustration of the mediating affects of subject control and coping on the relationship between stress and immune response, Laudenslager et al (1983) reports measuring the immunocompetence of rats subjected to inescapable electric shock, escapable shock, and restraint without shock. Rats in the escapable shock group were allowed to learn how to

turn off and control the shock, while the inescapable shock group were not allowed this option. Results illustrated suppression of PHA-induced lymphocyte proliferation in the inescapable shock group when compared with the unshocked control group, while the escapable shock group did not differ significantly from the unshocked control group. These find findings led the authors to suggest that the subject's perceived controllability over the stressor is a crucial variable in the modulation of immune response in a stressful situation (Laudenslager, 1983).

The importance of control in mediating the immune consequences of stress is supported by other animal studies. Mice when exposed to a single session of inescapable shock immediately after tumor cell implantation demonstrated a significant increase in the rate of tumor growth, while mice subjected to escapable shock showed tumor growth identical to the nonshocked control group (Sklar & Anisman, 1979). Similar responses to inescapable vs. escapable shock are reported by Visintainter et al (1982) citing a significant reduction in the incidence of rejection of transplanted non-syngeneric tumor cells in rats subjected to inescapable shock.

Ben-Eliyahu et al (1991) when replicating the Sklar & Anisman (1979) study found that the immediacy of the stressor introduction was crucial. The stressor had to occur immediately following injection of the tumor cells in order to produce the outcomes demonstrated by Sklar & Anisman (1979).

Somewhat contradictory results are reported by Mormede et al (1988), who indicates a decrease by one third of splenocyte reactivity to concanavalin A in rats exposed to two sessions of inescapable footshocks. This immune effect was completely reversed when each shock was preceded by a warning signal, despite the fact that serum corticosterone and prolactin were elevated in both conditions, suggesting a stress response. While these data provide support for the hypothesis that predictability of a stressor has strong mediating effects on its influence on immunity, the researchers were unable to explain why plasma corticosterone levels remained elevated in the escapable shock group.

In an early series of experiments, Mormede and associates (1984) demonstrated reduced splenocyte reactivity in yoked rats after 10 sessions of footshock,

but also showed reduced antibody response to sheep RBC's in the control group of rats who were allowed to avoid the footshocks. The mechanisms underlying these conflicting findings are unknown.

Summary of Animal Research Findings - Animal research on the mediating variables which affect stress and immune responses reveals that a variety of factors can alter a subject's response to a stressor. Animal research has revealed that the timing of the immune response measurement must coincide with the maximum expected effect of stress on immunity. A measurement taken too soon or too late will fail to demonstrate the expected immune consequences of stress. Chronicity and the intensity of the stressor has also been shown to be crucial in the measurement of stress induced immunosuppression. Animal studies have shown that a stressor must be of sufficient intensity and duration to first elicit a stress reaction in the subject in order to alter immune response. Stressors that cause weak, short-lived stress responses may fail to cause immune alteration, while chronic, prolonged stress response may result in adaptation and return to normal of immune responses.

A variety of subject variables have been shown to affect the stress/immunity link in animal studies. These include sex and species strain, subjects' age, subjects' need for social contact and subjects' ability to control the intensity and duration of a stressor. Stress/immunity studies of rats revealed males and certain species of rats were more susceptible to the immunosuppressive effects of stress. Age of the subject also appeared to be a factor in stress response and immunity, with older rats demonstrating less immunosuppression following stress than their younger counterparts. Species variations in response to a specific type of stressor was also illustrated in animal studies. The need for companionship was shown to be a potent stressor in certain species (monkeys) having broad immunosuppressive effects, while other species (rats) demonstrated immunoenhancement with isolation. Finally, an animal's ability to control the intensity and duration of the stressor proved a significant determinant in the occurrence of immunosuppression. Both mice and rats demonstrated normal or enhanced immune function when allowed control over the experimental stressor.

Application of Animal Research Findings to Human Studies - When designing either an animal or human study, care must be taken to identify when a stressor is expected to have its greatest affect on the subject's immune function. Measurement of both the stress response and the immune function must be timed to coincide with this point if credible results are to be obtained. Consideration must also be given to the intensity and chronicity of the stressor presented. A stressor of too little intensity will fail to elicit the desired effect, while a prolonged stressor can result in habituation and wipe out the desired outcome (Keller et al, 1991).

The issues of time between stressor onset and response measurement, and stressor intensity and chronicity explored in animal models are crucial to the traumatic injury experience in humans. As discussed earlier, serum cortisol levels rise quickly after injury in both moderately and severely injured patients, remaining elevated for days to weeks after injury (Jeffries et al, 1992). Severity of the injury (stressor) appears to affect the level of cortisol elevation, with more severe injury related to slightly less elevated cortisol levels (i.e. adrenal exhaustion) (Barton

et al, 1987). Timing of immune cell response is also critical. Lymphocyte subpopulations show a marked decrease in immunofluorescence (e.g.immunocompetence) during the first 24 to 48 hours post injury in all patients regardless of injury severity. This depression slowly resolved in subjects with less severe injuries, but persisted for days in the severely injured (Antonacci et al, 1984; Schluter et al, 1991). Similar results were seen with neutrophils (Babcock et al, 1990; White-Owen et al, 1992) and monocytes (Kruger et al, 1991), demonstrating a significant decrease in immunofluorescence of CD 11b and CD 14 receptors (respectively) immediately following injury (48-72 hours), persisting for days to weeks depending on the severity of injury.

Given these findings it is clear that the analysis of stress response and immune function following traumatic injury in humans must be timed to capture peak changes in measurement variables. Initial changes must be identified in the first 48 to 72 hours after injury, with late changes being captured 4 to 7 days later.

Subject variables like age, sex and psychological mediators must also be taken into account during the design

and implementation of both animal and human studies. Physiological differences occur in immune function and stress responsiveness as human subjects age, with older subjects demonstrating diminished immune response capacity (Sapolsky et al, 1986; Odio et, 1987).

Subject gender may also provide physiologic difference in the response to stress. Frankenhaeuser et al (1983) notes that male human subjects exhibit greater cortisol and catecholamine response to stress than females; while females appear to have less cardiovascular response to stress (Matthews & Stoney, 1988) and suffer less immune-related diseases (Fox, 1988; Adami et al, 1990).

While species strain is obviously not an issue in human studies, it does highlight the fact that subtle individual differences can have significant affect on a subject's response to the same stressor. Stress and immunity studies often utilize a matched-pair approach in subject selection in an attempt to control these individual differences.

Human Studies

While animal studies of stress and immunity provide increased experimental control and manipulation, they do not allow measurement of cognitive and emotional components. Human studies provide an opportunity to explore a wide range of mediating or intervening variables that act to alter the relationships between the stressor, stress response and immunity. Perceived control or the subject's perception of control over a stressor has been identified in the literature as a potential mediator in the stress/immunity relationship (Weisse, 1990; Wiedenfel et al, 1990; Cruse et al, 1992).

Subject Control - The mediating influence of perceived control on the effects of stress has been widely studied. Early studies consistently support the hypothesis that increased control reduces stress responses and increases well-being (Glass et al, 1971; Langer and Rodin, 1976; and Mills and Krantz, 1979). While investigators who manipulated control in more recent stress studies have failed to find consistent support for the hypothesis that perceived control reduces experimental stress (Padilla et al, 1981; Smith et al, 1986; Wallston, 1986), evidence

continues to suggest a link between these two variables (Affleck et al, 1987; Dennis, 1987; Kushner et al, 1992; McBride, 1993; Fitgerald, 1993; Kugler et al, 1994).

A subject's sense of control (perceived control) over a stressful situation has been implicated in both animal (Sklar & Anisman, 1979; Visintainer, 1982; Laudenslager et al, 1983; Maier & Laudenslager, 1988; Mormede et al, 1988) and human studies (Weisse, 1990; Wiedenfeld et al, 1990; and Cruse, 1992) as a powerful buffering factor in the stress/immunity relationship. As previously discussed, animal models have demonstrate decreased lymphocyte proliferation (Laudenslager et al, 1983), increased tumor growth (Sklar & Anisman, 1979), diminished tumor cell rejection (Visintainer et al, 1982), decreased splenocyte reactivity (Mormede et al, 1984, 1988) and impaired antibody response (Mormede et al, 1984) in rats subjected to uncontrollable stressors. Experimental situations which allowed the subject (human or animal) a measure of control over the occurrence, frequency or timing of the stressor were associated with significantly less stress response and immune dysfunction.

Human studies which have looked at the relationships between perceived control, stress and immunity are scarce. A review of the current literature reveals only two human studies that directly quantify perceived control and its affects on stress response and immunity (Weisse et al, 1990, Wiedenfeld et al, 1990). A third study of stress response and immune function following spinal cord injury, indirectly identifies perceived control (participation in a special rehabilitation program) as a modifying variable in this relationship (Cruse et al, 1992).

In a study of short-term noise and shock stress on 24 male subjects Weisse and associates (1990) demonstrated changes in mood, subjective stress levels and immune function following exposure to 30 minutes of mild electric shock and loud white noise administered in a random, intermittent pattern. Two groups were tested, with one groups allowed to control termination of the stressors, while the other group received an identical series of stressors they were not allowed to control. Mood, subjective stress response and immune function (lymphocyte proliferation to Con A and PHA; T and B cell, lymphocyte, monocyte and granulocyte percentages) were measured one

hour before and at 30, 50 and 150 minute intervals after each stress session. While subjects exposed to uncontrollable stress reported a change in mood (increased anger, frustration and a decrease in happiness from baseline), no decrease in immune function was seen. Conversely, while mood was not altered in the group allowed to control the stressor, immune function was decreased (reduced lymphocyte proliferation to Con A and decreased monocyte percentages after 90 minutes).

Weisse et al (1990) offers several explanations for the contradictory results of this study:

- *Timing of the measure in relation to the stressor.* The uncontrollable stressor may have been associated with a decrease in immune function, but insufficient time was allowed between the stressor and immune measurement to allow for this change to be observed.

- *Subjects with control over the stressor were required to expend more effort (i.e. more button pressing to terminate stressor) than subjects without control.* The number of button pushes was inversely related to immune function, suggesting the amount of effort expended and the arousal it caused may have acted to depress immune function.

- *Subjects with control reported feeling the shocks more strongly than subjects without control.* These perceptions of stronger shock were associated with decrease lymphocyte proliferation and lower monocyte percentages. Stressor control may have resulted in greater subjective perceptions of pain and discomfort and thus the observed decrease in immune function.

The results of this study point out the importance of stressor/response measurement timing and stressor intensity in study design. Unfortunately this study did not measure a physiologic correlate of stress response, such as catecholamines and/or cortisol, but the results of this study may be further explained by the work of Frankenhaeuser and associates on stress and control.

In a series of studies on the significance of control in stressful workplace situations (Lundberg & Forsman, 1979; Frankenhaeuser et al, 1980), two major components, effort and distress, are identified which define the response to stress. Effort is defined as an active means of coping involving elements of interest, engagement and determination. Distress is defined as a passive attitude of helplessness involving elements of dissatisfaction, boredom, uncertainty and anxiety. Effort and distress may be experienced alone or together in the same stressful situation and are associated with catecholamine and cortisol release. Frankenhaeuser et al (1986) suggest three ways in which these psychoneuroendocrine relationships can be conceptualized:

- *Effort with distress* - associated with an increase in both catecholamines and cortisol levels. A state typically seen with daily hassles of living, in which there is concerted effort to maintain control. Commonly seen in repetitive, highly routine tasks.

- *Effort without distress* - associated with an increase in catecholamine, while cortisol is often significantly decreased. A joyous state characterized by active, successful coping and high degree of subject control over the situation.

- *Distress without effort* - associated with a significant increase in cortisol and a possible elevation in catecholamines. A state typically seen in depressed patients, involving elements of passivity, helplessness, loss of control and giving up.

Based on these observations and conceptualizations Frankenhaeuser contends that a subject's endocrine response varies with the psychological significance of the situation, with cortisol demonstrating greater specificity in response to situational demands. Catecholamines are more general in their response, increasing during pleasant as well as distressing situations.

Frankenhaeuser further contends that control is an important modulating variable in the attempt to achieve a state of "effort without distress". She proposes that a lack of control is associated with feelings of distress, while a sense of control stimulates effort and decreases

negative feelings. Thus as control changes the balance between effort and distress, it also affects the release of catecholamines and cortisol.

Findings from two studies support Frankenhaeuser's hypothesis. A group of students were placed in a low-control situation requiring the subject to press a key in response to a set of weak light signals of randomly occurring intensity (Lundberg & Forsman, 1979). The situation was highly monotonous and unpredictable. Self-report measures demonstrated that this low-control task resulted in subjects' feelings of both effort and distress, associated with an increase in both adrenaline and cortisol levels.

When the same group of students were placed in a high-control situation allowing the subject control over the experimental light stimulus to maintain an optimal pace throughout the session, an "effort without distress" state was demonstrated (Frankenhaeuser, 1980). Subjects reported being pleasantly challenged, perceiving themselves in complete control and motivated to complete the task. Neuroendocrine responses were as predicted, following an

"effort without distress" pattern, showing an increase in adrenaline levels, but a decrease in cortisol levels.

Given Frankenhaeuser's conceptualization of effort and distress in response to stressful situations it is possible to offer another explanation for Weisse's (1990) contradictory results in the study of controllable and uncontrollable stress and immune function. While neuroendocrine response was not measured, the experimental design of this study may have created a state of "effort with distress" in subjects with control (i.e. effortful button pushing was associated with increased subjective pain and discomfort, elevating both catecholamines and cortisol levels). This dual increase in neuroendocrine hormones would account for the unexpected immunosuppression seen in the subjects with control.

A final explanation for the results seen in this study may be due to the selection of immune function tests which fail to reflect the changes induced by a short term stressor. While the immune effects of increased epinephrine upon lymphocytes occur within minutes and disappear within two hours (Crary, 1983), the affect of increased cortisol takes much longer to achieve, especially

on monocyte populations (Munck & Guyre, 1991). Thus the measures utilized and the cell populations examined may have failed to reflect later immune changes. A more appropriate measure for this study might have been natural killer cells which have produced the most consistent response to short term stress (Kiecolt-Glaser et al, 1992).

In a recent study of phobic subjects with a history of severe fear reactions to snakes (Wiedenfel et al, 1990), cortisol and catecholamine levels were obtained along with percentages of lymphocytes and T cells, interleukin-2, and HLA-DR levels before, during and after the introduction of a series of graded coping tasks (looking at snakes from distance, touching snakes, etc.) intended to mediate their stress response to experimental snake exposures. It was noted that subjects who demonstrated a rapid acquisition of self efficacy in dealing with the threatening snakes (able to handle snakes with ease), evidenced an elevation in catecholamines and a significant increase in immune function or immunoenhancement. Subjects who were slower to achieve a sense of self efficacy in their dealings with the snake threat, also demonstrated prolonged elevations in salivary cortisol and immunosuppression. These findings

led researchers to suggest that rapid acquisition of perceived control may be associated with activation of the sympathetic nervous system (catecholamine release) or "effort without distress" as defined by Frankenhaeuser, while slow activation of perceived control may be associated with cortisol release or "distress without effort".

Interesting immune changes were demonstrated in a study of 34 spinal cord injury and stroke patients receiving physical therapy that involved sensory stimulation of peripheral nerves in the affected extremities (Cruse et al, 1992). The researchers report an initial decrease in natural killer cell activity two weeks after injury which was accompanied by increased plasma ACTH and urine free cortisol levels, as compared to normal levels found in the control (noninjured) group. Lymphocyte transformation and interleukin-2 levels were diminished at three months post injury, while control subjects demonstrated normal levels. Six month after injury NK and lymphocyte levels were restored to normal in the injured group. This restoration of immune function was associated with participation in a specific physical therapy program

which included biofeedback to the central nervous system using electrical stimulation of peripheral nerves. Five injured subjects who received no physical therapy continued to demonstrate NK impairment six months after injury.

While perceived control was not measured in this study, researchers did note that a progressive improvement in functional independence, as measured by the *Functional Independence Measure,* paralleled the restoration of immune function in the 34 subjects studied. Although study researchers attribute the improvement in immune function to the electrical stimulation of the central nervous system, these results also suggest the subjects' increased sense of perceived control over their situation may have been a factor. As subjects began to see improvement in their physical status secondary to the physical therapy, it is likely their sense of perceived control would also increase. This increased perceived control may have been associated with the immune changes seen. Further study is necessary to support this hypothesis.

Summary of Research Findings on Stressors and Mediators

The studies just reviewed indicate that certain types of stressors invoke definite patterns of stress and immune response. Long-term, chronic stressors like bereavement, clinical depression, loneliness, and marital discord were most commonly associated with increased subjective stress, increased anxiety, depression, increased urinary cortisol, decreased lymphocyte proliferation and lower total T and B cell numbers. Short-term experimentally induced stressors like exam stress were most frequently associated with increased catecholamine levels, mild to moderate subjective stress, frustration, anger, increased natural killer cell activity and increased suppressor/cyctoxic cell numbers. Immune changes occurred quickly after short-term stress and rapidly returned to normal upon termination of the stressor. Long-term stressors evoked immune changes which were sustained for days to months.

A number of studies reviewed implicated study design issues like intensity and chronicity of stressors and subject variables such as age, sex, species strain,

isolation, coping and controllability as important mediating or intervening variables in the stress and immunity relationship.

Finally, it was shown that traumatic injury is a potent stressor which leads to significant immune function changes. Despite extensive investigation, the mechanisms underlying this relationship remain unclear, while studies exploring the psychological implications of stress and immunity following traumatic injury are lacking.

Gaps in the Literature

Little is known about the psychological implications of traumatic injury and/or the affects psychological responses have on the victim's physiological status. The few psychological studies that have been done have focused on powerlessness in critically ill patients (Boeing et al, 1989; Roberts et al, 1990); environmental stressors in the ICU (Ballard, 1981); control interventions (Dennis, 1987); and perceptions of control after planned surgery (Linn et al, 1988; Fitzgerald et al, 1993; Kugler et al, 1994). Two studies focused on perceived control of recovery after physical injury (Ferington, 1986; Partridge et al, 1989).

While these studies examined elements of control, i.e. preference for control (Ferington, 1986) and Locus of Control (Partridge et al, 1989), neither of these studies looked at the influence these variables might have on a physiological process such as immunity.

Similar results were revealed when examining the literature on post-injury immunosuppression. While extensive evidence was found to support links between injury, elevated serum cortisol levels (Hume et al, 1956; Meguid et al, 1974; Stoner et al, 1979; Vaughan et al, 1982; Frayn et al, 1983; Barton et al, 1987; Woolf, 1992) and immune suppression (Cupps et al, 1984; Calvano et al, 1984, 1986, 1987, 1988; Antonacci et al, 1982, 1983, 1984), no studies were found which document the effects of psychological variables following injury. Further, the inter-relationships between these variables (traumatic injury, stress response, perception of control and immunity) have yet to be explored and/or documented.

CHAPTER III

METHODOLOGY

Research Aims and Questions

The purpose of this study was to examine the relationships among perceived control, stress response and immune response following traumatic injury. The specific aims of this study were to:

- Examine whether significant relationships existed between perceived control, subjective and physiologic stress response, and immune response following traumatic injury.
- Determine whether these relationships change over time at early (48 hours) and late (96 hours) post-injury.

The following research questions were posed to explore the specific aims of the study:

- Do subjects sustaining traumatic injury experience changes in perceived control, subjective and physiologic stress response and immune response between early (48 hours) and late post-injury (96 hours)?
- Is immune response at early post-injury (48 hours), related to subjective stress response; physiologic stress response; and/or perceived control at early post-injury (48 hours)?
- Is immune response at late post-injury (96 hours), related to subjective stress response; physiologic

stress response; and/or perceived control at late post-injury (96 hours)?

- Is immune response at late post-injury (96 hours), related to subjective stress response; physiologic stress response; and/or perceived control at early post-injury (48 hours)?

Assumptions

- Traumatic injury is perceived as a significant psychological and physiological stressor by the trauma victim.
- Following a traumatic injury, subjects experience a change in perceived control over their injury and the events surrounding it.
- Pencil and paper tests can accurately measure a subject's psychological state at a given point in time.
- Subjective stress response can be accurately measured by a pencil and paper test.
- A subject's sense of perceived control can be accurately measured by a pencil and paper test.
- Serum cortisol values obtained during the lowest level of it's diurnal cycle, are an accurate reflection of physiological stress response.

- The intensity of CD (cluster determinant) antigen expression on immune cell membrane surfaces is a valid measure of cellular response and immunocompetence.
- Immunofluorescence of CD 25 on lymphocytes, CD 11b on granulocytes and monocytes, CD 16 on granulocytes and CD 14 on monocytes are valid representatives of cellular immune response in these populations.

Definitions of Terms

Psychological Stress Response

Stress - "A state which arises from an actual or perceived demand-capability imbalance in the organism's vital adjustment action and which is partially manifested by a nonspecific response" (Mikhail, 1981, p14).

Stressor (Activator) - internal and external environmental events or conditions that change an individual's present state and is sufficiently intense or frequent to create significant physical or psychosocial reactions (Elliot & Eisdorfer, 1982). Five types of stressors are defined by Elliot and Eisdorfer (1982):

- acute - time limited stressors (e.g. awaiting surgery, unpleasant surprise, life-threatening illness).

- stressor sequences - series of stressors that occur over time (e.g. divorce, separation)
- chronic, intermittent stressors - conflicts that occur on a regular basis (e.g. family conflicts)
- chronic stressors - occur over long period of time and may or may not be initiated by a discreet event
- daily hassles - minor problems that continue to pile up and annoy (e.g. traffic jams, deadlines)

For the purpose of this study traumatic injury and the subsequent hospitalization that followed it was conceptualized as an acute stressor which elicited a stress response in the study subjects.

Stress Response - Response to a stimulus or stressor that is an adaptive mechanism, reflected in both physiological manifestations and psychological alterations which are interrelated and connected (Guzzetta, 1979). Stress response was conceptualized in this study as having two components; a psychological response (subjective stress) and a physiologic response (elevation in plasma cortisol).

Mediator - Defined by Elliot and Eisdorfer (1982), an intervening variable that filters and modifies each stage in the stress response process and can be biological,

psychological, environmental, or social in nature. A mediator can also be a personal characteristic such as cognitive appraisal, coping or sense of control. It is further defined by its intensity, quantity (magnitude), and temporal pattern (duration, frequency). In this study perceived control was theorized to be a mediator in the relationship between the stressor (traumatic injury) and the stress response (subjective assessment and plasma cortisol).

Consequences - Long-term adaptive changes or sequellae that can be defined on a variety of organizational levels such as; physiological (e.g.immunosuppression), psychological (e.g. depression) and sociological (e.g. social isolation). They also display the characteristics of intensity, quantity, and temporal pattern, along with an evaluative quality of being either "bad or good" outcomes (Elliot & Eisdofer, 1982). For the purposes of this study, change in immune cell response (up-regulation or down-regulation) was theorized to be a consequence of increased stress response.

Psychological Response

Perceived Control - Wallhagen defines perceived control as the "perception that salient or valued aspects of one's life are manageable" (Wallhagen, 1990, p. 32). Utilizing this definition perceived control is based on a balance between perceived environmental demands and perceived available resources. Whether or not these beliefs are grounded in reality or whether the subject is actually in control of the situation or not is of little importance, only that the subject believes or perceives a sense of control over the current situation.

For the purposes of this study, perceived control was defined as the sense of control a subject currently felt over their traumatic injury.

Immune Response

Cluster Determinants - Cluster determinants (CD) are groups of cell surface proteins (antigens) on leukocytes that are uniquely distinguishable with monoclonal antibodies. The patterns of CD display can be used to differentiate cell populations. Specific cellular

functions have been linked to certain receptors (e.g. CD25 on activated T-cells, receptor for IL-2), while others remain undetermined.

Cell Phenotype Immunofluorescence - A monoclonal antibody coupled with a fluorescent dye is used to identify cell surface antigens on leukocytes. These stained cells are then examined for fluorescence using flow cytometry. The quantity of fluorescence correlates directly with the quantity of CD antigen expressed on the cell surface. This technology thus allows accurate quantification of fluorescence for each cell and determines the distribution of CD antigens within the sample population. Utilizing this approach and other information based upon cell size and granularity, specific types of cells (granulocytes, monocytes, lymphocytes) can be identified.

Flow Cytometry - Analogous to the visual examination of immunofluorescent stained cells under a ultra-violet microscope, continuous flow cytometry allows examination of 10,000 individual cells in 1 to 2 minutes. Cells in liquid suspension are injected into a fluid sheath and individually lined up before a series of laser lights. Light refracted off each cell is collected by a

photomultipier and an electrical impulse generated. This is digitized and analyzed by an attached computer. Results are displayed as distinct populations of cells on data plots which can be isolated and analyzed.

Flow Cytometry Gating - A numerical or graphical boundary (region) that defines a subset of cells, allowing analysis of specific groups of cells.

Flow Cytometry Histogram - A graphical means of presenting single-parameter (e.g. CD11B on monocytes) data output from flow cytometry. The horizontal axis of the graph represents the increasing intensity of the parameter, and the vertical axis represents the number of events displaying discrete values of intensity.

Immune Functional Response - The final outcome measurement of immune cell responsiveness (CD expression) to a specific cell stimulant. Immune cell responsiveness is either increased (enhanced) or decreased (suppressed), depending on the current ability of the cell surface CD antigens to respond when challenged by a stimulant.

Research Design

A repeated measures design was used to investigate the relationships among perceived control, stress response and immune response following traumatic injury. Subjective and physiologic data were collected at two time intervals as outlined in the Study Timeline (Appendix A): early (48-72 hours) and late (96 hours) post injury.

Research Setting

The study was conducted at the Mary Martin Trauma Center at San Francisco General Hospital and Medical Center (SFGH). The Trauma Center is an urban Level I trauma center that treats between 100 and 150 trauma patients per month. Six subjects were initially enrolled in the study while in the ICU, with a sample mean of 1.8 days in ICU (SD 1.8). The remaining four subjects were never admitted to the ICU, but went directly to the surgical floor on admission and were recruited to the study there.

Sample

Study Subjects - Potential subjects were identified from the daily trauma admission log. All trauma patients

who met study admission criteria were considered for study inclusion with initial subject selection based on the level of injury severity (*Injury Severity Score - ISS*) as calculated by the *Abbreviated Injury Scale (AIS)* (Appendix B) (Association for the Advancement of Automotive Medicine). Subject demonstrating an ISS greater than or equal to 9 (as calculated by the principal investigator) were included in the sample. Inclusion criteria also required that subjects were able to speak and understand English, had traumatic injuries sustained no longer than 48 hours prior to the first data collection point and were alert and responsive with a cognitive function at Level VII or greater as determined by the *Rancho Los Amigos Level of Cognitive Functioning Scale* (CFS) (Appendix B) (Hagen, 1981). Seven males and three females between the ages of 19 and 77 were recruited.

Subjects were excluded from the study who demonstrated altered mental status, were currently receiving steroid therapy, had known HIV or other blood borne viral disease and/or were pregnant or under 18 years of age.

Normal Subjects - In order to fully characterize the immunologic data obtained from trauma subjects during data

collection, nine normal, healthy volunteers (normals) were selected to donate blood for analysis using the study's immune response protocol. Blood was drawn from five female and four male volunteers who ranged in age from 23 to 53 and reported no exceptional life stress. All normals reported excellent health and no risks factors for immunosuppression (i.e. HIV positive or other blood borne viral diseases). Blood was drawn once, using the same time frame and techniques as outlined in the study protocol for study Subjects. All samples were prepared and analyzed using the same protocol as described previously for immune function analysis.

Protection of Human Rights

Approval from the Committee on Human Research at the University of California, San Francisco was obtained prior to initiation of the study. The study, procedures, risks and potential benefits were explained to all prospective participants and written consent was obtained. Strict confidentiality was maintained with the handling of all subject information obtained from hospital records. All data pertaining to subjects was kept in locked files in the

Surgery Office at SFGH and all computer files were password secured. No individual identities were used in study reports.

Variables and Instrumentation

The key variables in this study were: perceived control, subjective stress response, physiologic stress response and immune response. Other variables included illness and injury severity, pre-study cognitive function and pre-study immune status. Each variable was measured by a valid, appropriate instrument or method as listed in Table 2.

TABLE 2. STUDY VARIABLES AND CORRESPONDING MEASURES.

VARIABLE	MEASURE	APPENDIX/ PAGE
Subjective Stress Response	Stress/Arousal Checklist Stress/Arousal Visual Analogue Scale	B/p.89
Physiologic Stress Response	Serum Cortisol	p.91
Perceived Control	Wallhagen's Experience of Current Situation Subscale	B/p.94
Injury Severity	Abbreviated Injury Scale (Injury Severity Scale, ISS)	B/p.95
Illness Severity	APACHE II	B/p.97
Pre-Study Cognitive Function	Rancho Los Amigos Cognitive Function Scale	B/p.98
Pre-Study Immune Status	Delayed Type Hypersensitivity Skin Tests	p.99
Immune Response	Cell Phenotype Differentiation	p.101

Subjective Stress Response

Subjective stress response was measured by the Stress/Arousal Check List(SACL) (Appendix B) which is designed to measure both stress response and arousal using a 20 item mood adjective list rated on a 4-point Likert scale. King et al (1987) contends that arousal is an emotional state which fluctuates according to demand and appears to relate to the individual's utilization of resources to cope with the demand. Stress is a negative

emotion which is more strongly associated with the individual's doubts about his coping ability. King states stress and arousal are independent measures of mood which can be expressed as correlation coefficients, meaning that some individual with high stress levels will demonstrate low levels of arousal, while other subjects' stress and arousal will vary in unison. King suggest this range of individual differences can be clearly demonstrated by the use of a repeated measures design (King et al, 1987).

Based on research with a variety of English-speaking subjects in both Australia and England, King et al (1987) contents that the SACL and its accompanying visual analogue scale demonstrate sufficient robustness to justify its use with other English-speaking populations without significant changes to the scales psychometrics. The researchers further contend that this revised, shortened version of the SACL scale demonstrates strong validity and reliability when compared to the original scale (Cox, 1978) and other measures of stress (Thayer, 1967).

Stress response is measured in the SACL by 20 items and arousal by 14 items and demonstrates an alpha reliability of 0.96 for the stress scale and 0.96 for the

arousal scale. A final score for each factor is obtained by totaling scores given for each adjective with a reported normative stress mean of 1.7 and a standard deviation of ± 2.0 (King et al, 1987). A normative arousal mean of 7.3 and a standard deviation of ± 2.2 is reported (King et al, 1987).

Two 10 cm visual analogue scales are included at the end of the SACL, that measure dichotomous variables of stress and arousal. Developed by King et al (1987) to provide a quick assessment of stress and arousal, the scale demonstrates a normative mean value on the stress line of 4.5 cm, ± 2.6 cm and 5.1 cm ± 2.7 cm on the arousal line. A correlation coefficient of 0.83 was demonstrated between the stress line and the stress scale, while a similar correlation of 0.83 was seen between the arousal line and the arousal scale (Cox et al, 1978; Mackay et al, 1978; King et al, 1983; 1987).

Physiologic Stress Response

The physiologic stress response of subjects was determined by serum cortisol. Serum cortisol is regulated by the secretion of corticotrophin-releasing factor (CRF)

and adrenocorticotropic hormone (ACTH) and because of their diurnal variation in secretion, serum cortisol also demonstrates a distinct diurnal pattern which correlates with the basic biologic circadian rhythm. Plasma cortisol is maximally secreted between 4:00 AM and 12:00 PM and drops to its lowest levels between 3:00 PM and 5:00 PM (Pagana et al, 1982). Tepperman and Tepperman (1987) cite a normal secretion rate of 20 - 25 mg/day for plasma cortisol, with a diurnal variation of 4 to 16 µg/dL. Cortisol is transported in the blood bound either to corticosteroid-binding globulin (CBG) by a high affinity bond or loosely bound to albumin. Plasma cortisol can be measured by either radioimmunoassay (RIA), liquid chromatography or fluorescence polarization immunoassay techniques. While liquid chromatography is noted to be more accurate in detecting low levels of cortisol (Oka et al, 1987) it requires a laboratory with specialized equipment and highly trained personnel. The more widely used RIA method can be applied by the average researcher and has demonstrated excellent results with higher levels of cortisol (Oka et al, 1987).

The recently developed fluorescence polarization immunoassay has demonstrated good reliability when compared with the more standard RIA method and has the added advantages of being totally automated, highly accurate, cost-effective, quick and convenient (Ayers et al, 1989).

For the purposes of this study, serum cortisol assays were conducted by the University of California, San Francisco, Department of Laboratory Medicine at San Francisco General Hospital. Blood specimens were collected from subjects in a 5 cc red top test tube, placed on ice and transported immediately to the laboratory for analysis utilizing the Abbott TDxFLx Cortisol Assay.

The Abbott TDxFLx Cortisol Assay is a competitive-binding assay which uses fluorescence polarization immunoassay technology. Cortisol antigen in the subject's blood sample competes with a cortisol fluorescent tracer for sites on a cortisol antibody. The fluorescently labeled complex is then excited with plane polarized light. The change in polarization of the fluorescent light emitted by the tracer is inversely proportional to the concentration of cortisol in the subject's blood (Department of Clinical Medicine, 1992). SFGH's Department

of Laboratory Medicine control reference ranges for serum cortisol results were as follows:

2 - 23 µg/dL (138 µmol/L) 8:00 AM to 9:00 PM
5 - 13 µg/dL (138-359 µmol/L) 4:00 PM to 5:00 PM

Since the results of serum cortisol are affected by coffee, caffeine, smoking, aspirin, acetaminophen, morphine, barbiturates, reserpine, furosemide, monoamine oxidase inhibitors and spironolactone, use of any of these agents were noted and subjects cautioned against and questioned about any smoking or coffee drinking within two hours prior to blood sampling.

Perceived Control

Subjects' sense of perceived control over their traumatic injury and subsequent hospitalization was measured using a subscale of Wallhagen's Revised Perceived Control Questionnaire. Comprised of 13 items, Wallhagen's Experience of Current Situation Subscale (Appendix B), is designed to measure a subject's sense of manageability (one can handle the demands of a situation) (Wallhagen, 1995). Utilizing a forced choice Likert-type scale subjects are asked if they agree or disagree with each stem question and

then whether they agree/disagree strongly or moderately. Responses are graded on a 1 - 4 scale, with a possible score range of 13 to 52. Responses were reverse coded so that low scores (13-32) reflected low levels of perceived control, while high scores (33-52) represented high levels of perceived control.

The original 20 item Revised Perceived Control Questionnaire demonstrated an alpha reliability of 0.93. The revised 13 item subscale, which used positive response items from the original scale, demonstrated an alpha reliability of .86 (Wallhagen, 1995).

Injury Severity

Initial subject selection for the study was based on determination of the level of injury severity utilizing the Abbreviated Injury Scale (AIS)(Association for the Advancement of Automotive Medicine, 1985). The AIS (Appendix B) was first developed by the American Medical Association's Committee on Medical Aspects of Automotive Injury and was originally designed to grade the severity of injury in automobile accident victims. Subsequent revisions in the tool have resulted in an instrument that

can be used to assess severity of injury in all types of trauma patients. Currently the tool can grade both blunt and penetrating trauma and can capture over 1,200 injury descriptions. A revised version of the tool was developed for easy clinical use. This one page condensed form has shown a 95% accuracy in use in a Level I Trauma Center (Champion et al, 1988) and is currently in wide general use.

The AIS tool incorporates assessment of injury in six anatomical areas (head/neck, face, thorax, abdomen, extremities and external) which are rated on a 1 to 5 ordinal scale (1= minor to 5= critical, survival uncertain) resulting in six individual AIS scores, each of which is squared. The three highest, squared AIS scores are added together to obtain a total Injury Severity Score (ISS). A score of 1 to 75 is obtained on the final ISS, with the rate of mortality rising as the score increases. Champion et al (1988) in an analysis of 33,308 trauma patients from 89 hospitals in the United States and Canada demonstrated an increase in mortality that correlated with an increase in injury severity score. A 50% mortality was reported with an injury score of 40 or greater, while moralities of

25% and 10% were reported with scores of 25 and 15 respectively. Dunham and Gens (1986) report that the Injury Severity Score explained 22% of the variance in mortality when compared to other instruments of severity scoring.

Illness Severity

Along with an assessment of injury severity, subjects were also evaluated for illness severity utilizing the APACHE II (Acute Physiology and Chronic Health Evaluation) (Appendix B), a widely used severity scoring instrument.

The APACHE II is the most recent version of the original APACHE tool which was initially comprised of 34 physiologic variables designed to quantify severity of acute disease in the intensive care setting. Revised by Knaus et al, (1988) the APACHE II is comprised of 12 variables including; temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, white blood count, and the Glasgow Coma Scale (a measure of neurological function). Each variable receives a subscore which is weighed and totaled to achieve

a final Acute Physiology Score (APS). Because age and severe, chronic health problems affect physiologic reserve, they are also scored and added to the APS. The maximum possible score is 72, but Knaus et al (1988) reports no patient demonstrating a score over 55.

In a study of 5,814 ICU admissions a direct relationship between APACHE II scores and observed hospital death rates is reported (Knaus et al, 1988). For every 5 point increase in the APACHE II score a significant increase in death rate was see (e.g. a 73% death rate for patients with a score of 30 to 34 points, while an 84% death rate was seen with a score of 35 or more).

Pre-Study Cognitive Function

The Rancho Los Amigos Cognitive Function Scale (CFS) (Appendix G) was used in this study to determine the level of subject awareness and cognitive functioning prior to administration of subjective perceived control and stress tools which require a moderate measure of concentration and focused thinking. Subjects were required to achieve a score of at least seven (automatic and appropriate response, appears oriented within hospital setting) at each data

collection point in order to be included in the study. All subjects demonstrated a score of seven or higher at both time points.

The CFS was developed by an interdisciplinary team based on the observations of 1,000 traumatic brain injured patients (Hagen et al, 1979). It is an eight level behavioral rating scale designed to assess cognitive function based on the assumption that observations of the type, nature and quality of the subject's behavioral responses can be used to estimate the cognitive level of functioning. It has been used nationwide for approximately 20 years and demonstrates an inter-rater reliability ranging from .87 to .94 and test-retest reliability of .82. Concurrent validity of .92 has been shown with a similar instrument, the Stover-Zeigler Scale (Flannery, 1993).

Pre-Study Immune Status

In order to determine subjects' immune status prior to study enrollment, a panel of delayed type hypersensitivity skin tests (tuberculin purified-protein derivative - PPD and candida extract) were administered to the subjects on

the day of study enrollment. Skin test results were read at 48 and 72 hours post-placement.

The delayed type hypersensitivity skin test or DTH is the oldest and simplest test of cell-mediated immunity. Utilizing intradermal injections a panel of antigens are injected into a subject's forearm. Common antigens used include Candida extract, histoplasmin, coccidiodin, mumps, tuberculin purified-protein derivative (PPD), and streptokinase- streptodornase (SKSD). Introduction of these foreign antigens challenges the subject's antigenic memory stimulating previously sensitized antigen-specific T cells causing them to release lymphokines. In turn, these lymphokines initiate an accumulation of macrophages, increase blood flow, increase permeability, instigate the coagulation and kinin cascades and enhance macrophage activity at the site of injection. This results in an area of induration and erythema surrounding the skin test site (wheal). Reading of the results is done after 48 hours by comparing the size of the subject's wheal to a control wheal. Positive results (significant induration) indicate an effective and competent T lymphocyte response. A negative result in a subject who has had prior exposure to

the antigen used for testing suggests a state of immunodysfunction or "anergy" (Widmann, 1989; Ogle et al, 1989).

An anergy (nonreactive) reaction to standard skin tests has been associated with abnormal lymphocyte migration, chemotaxis and function in surgical patients. It has also proven to be predictive of sepsis development in a wide variety of surgical and trauma patients (Meakins, 1988).

Immune Response

As described earlier, most traditional methods of measuring immune response are time-consuming, labor intensive and expensive. For the purposes of this study cell phenotype differentiation was selected as the measure of choice because of its ease of application, rapid results and specificity of information regarding large numbers of cells (Sigal and Ron, 1994). As leukocytes mature they acquire specific surface antigens on their membranes, linked to the cell via an antigen receptor. These "cluster determinants" (CD) have been identified and classified using monoclonal antibodies which are highly specific and

bind only with their target antigens. As specific antigens have been identified it has been possible to map their distribution on cell subpopulations linking them with specific cell functions (Widman, 1989).

Monoclonal antibodies can be labeled utilizing immunofluorescent dyes or fluorochromes which emit light of a specific wavelength when excited by exposure to light of a shorter wavelength. These fluorescently labeled monoclonal antibodies can then be used to localize specific antigens on cell surfaces using flow cytometric analysis (Widman, 1989).

In flow cytometry (Figure 5) the cells under study are placed in a dilute suspension and ejected through an aperture into the center of a continuously flowing fluid sheath. This fluid sheath acts to constrain the cell suspension, forcing the cells to line up single file and pass in front of a laser light beam one at a time. As a cell passes in front of the laser light it deflects light in all directions. This deflected light is then picked up by a detector system of lens located forward to the laser beam (forward light scatter - FSc) and at right angle to the laser beam (side scatter - SSc). The refracted light

emitted from the fluorescent cells is then amplified in a series of photomultiplier tubes designed to detect green (Fluorescein isothiocyanate - FITC), orange (Phycoerythrin - PE) and violet (TRI-COLOR™) fluorescence at specific peak emission (525nm, 575nm and 667nm, respectively). An electrical impulse is generated, digitized, stored and analyzed by a computer providing information on the individual cell's relative size, fluorescence intensity and granularity or internal complexity (Hudson et al, 1989).

Utilizing these parameters lymphocytes, monocytes and neutrophiles can be differentiated and their level of fluorescent activity quantified (i.e. CD expression) (Widman, 1989). The mean fluorescence (MF) for each CD marker is recorded for 10,000 sequential cells and compared to standards to allow for intra-subject comparison of data. The MF correlates directly with the surface expression of the particular determinant.

For the purposes of this study the mean fluorescence of four monoclonal antibody markers (CD 11b, 14, 16 and 25) were assessed on three types of cells (lymphocytes, granulocytes and monocytes). These markers were selected for the study because each has been linked to a specific

cell function (i.e. CD 11b on neutrophils = complement cascade) and have received extensive study. All monoclonal antibodies used in the study were supplied by Caltag Laboratories.

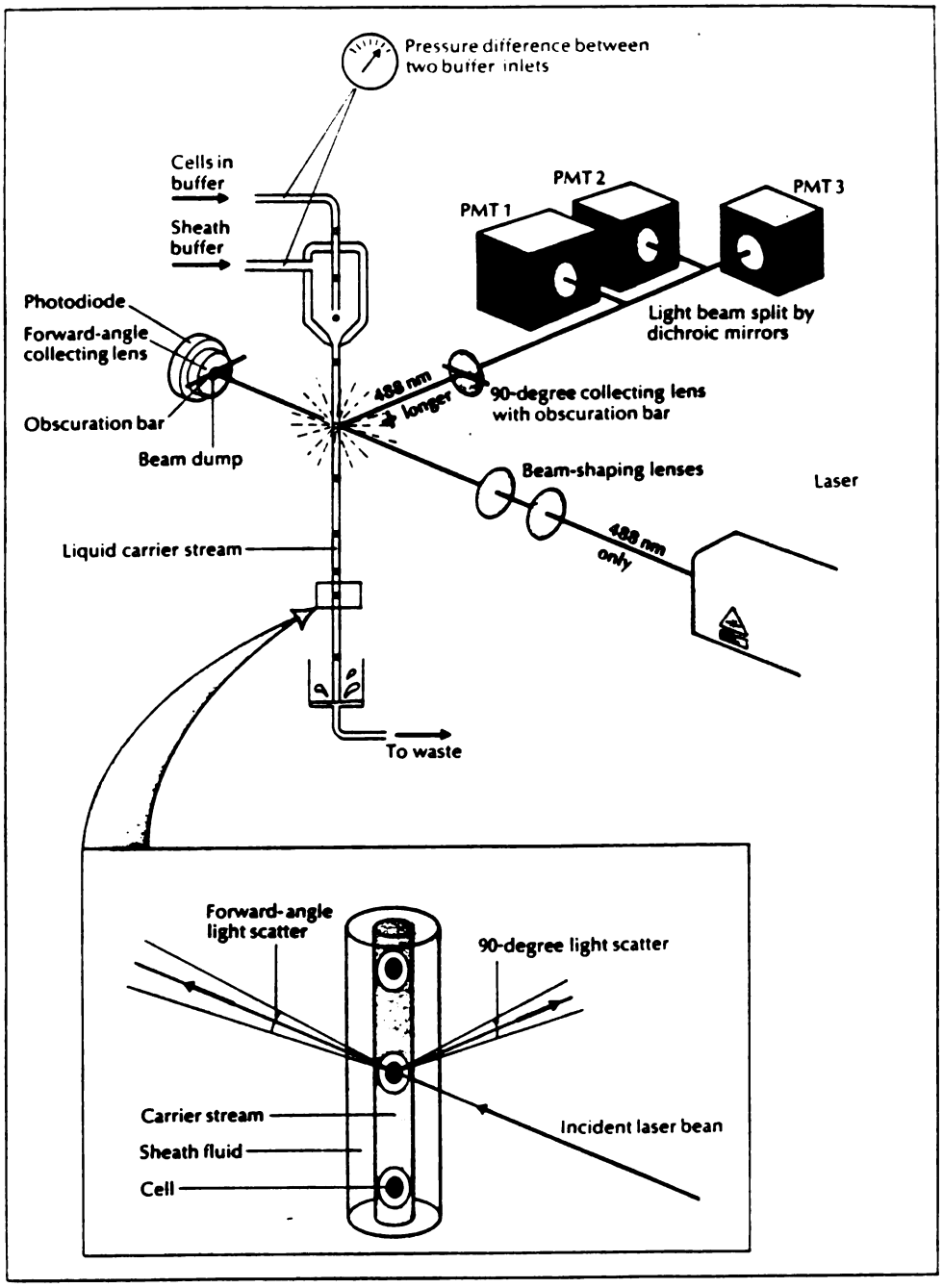


FIGURE 5. MECHANISMS OF CELL FLOW CYTOMETRY

From "The Lymphocyte: Its Role and Function" by L. Hudson and F. Hay. 1989, *Practical Immunology*, p. 119. Copyright 1989 by Blackwell Scientific Publications. Reprinted by permission.

Study Materials

Monoclonal Antibodies

Monoclonal antibody anti-CD 11b - recognizes a human leukocyte antigen (CR_3) that is the receptor for C3bi, part of the complement system. The CD 11b antigen is present on approximately 30% of peripheral blood lymphocytes and mature neutrophils, eosinophils and monocytes. Neutrophils expressing CD 11b+ receptors have been shown to have active adhesion and phagocytosis properties, while CD 11b- neutrophils demonstrate significant reduction in these properties (White-Owen et al, 1990).

The importance of the CD 11b on neutrophils as a measure of immunity is illustrated by studies which have shown marked reductions in the percentages of CD 11b+ neutrophils following severe burn and traumatic injury (Babcock et al, 1990; White-Owen et al, 1992).

A study of 34 severely burned patients, conducted by Babcock et al, (1990) revealed a relationship between the decrease in percentages and absolute numbers of CD 11b+ neutrophils and the increased incidence of infection and sepsis. While the percentage of CD 11b+ neutrophils was

significantly decreased in all burn patients, when compared to normal subjects, it was also noted that the occurrence of sepsis was closely linked to the amount of decrease in CD 11b+ neutrophils in individual subjects.

Increased injury severity (APACHE II) negatively correlated with diminished expression of CD 11b+ cells in a study of 27 severely injured trauma patients (White-Owen et al, 1992). Subjects demonstrating APACHE II scores of 19-25 consistently displayed less CD 11b+ neutrophils (35%), at three data collection points (Weeks 0,1,3), while subjects with APACHE II scores of 10-18 showed CD 11b+ neutrophil percentages of 68% at the same time intervals.

For the purposes of this study, anti-CD 11b linked with the immunofluorescent dye FITC, with an excitation wavelength of 488nm and a peak emission wavelength of 525nm, was used to identify CD 11b on granulocytes and monocytes. The negative isotype (negative control comprised of identical IgG isotype, directed against non-human antigens to assess non-specific baseline binding to leukocytes) for CD 11b is Mouse IgG-1 (Caltag Laboratories, 1993).

Monoclonal antibody anti-CD 16 - is specific for the low affinity IgG Fc receptor, FcγRIII (part of the complement process), found on the surfaces of approximately 85% of granulocytes (neutrophils, eosinophils, basophils and mast cells)(Roitt et al, 1989). It is also believed to be important to bacterial phagocytosis (White-Owen et al, 1992). Approximately 5% of granulocytes fail to express the CD 16 receptor and are thus CD 16-.

Expression of CD 16 on neutrophils was also measured, along with CD 11b, in the two studies by Babcock et al (1990) and White-Owen et al (1992), discussed above. Similar results were reported with a decrease in the percentage of CD 16+ neutrophils (68% to 35%) related to the severity of injury (White-Owen et al, 1992) and the incidence of sepsis post injury (Babcock et al, 1990).

For the purposes of this study, anti-CD 16 conjugated with the immunofluorescent dye PE, with an excitation wavelength of 488nm and a peak emission wavelength of 575nm, was used to identify CD 16 on granulocytes (Caltag Laboratories, 1993). The negative isotype for CD 16 is IgG-1 (Caltag Laboratories, 1993).

Monoclonal antibody anti-CD 14 - recognizes a monocyte/ macrophage antigen, Mr 55 kDa. This antigen is present on 70% to 93% of normal peripheral blood monocytes and while its function is undetermined, it has been related to myeloid growth factors (Haziot et al, 1988) and as a cell membrane receptor for lipopolysaccharide (LPS or endotoxin) (Kruger et al, 1991). Anti-CD 14 does not react with unstimulated lymphocytes, mitogen-activated T-lymphocytes, erythrocytes or platelets (Haziot et al, 1988).

Because CD 14 on monocytes can serve as a receptor for endotoxin (a component of Gram-negative bacteria) when it is combined with lipopolysaccharide binding protein (LPS), it has been implicated as precipitating the cascade of events preceding the development of the inflammatory process (Morrison et al, 1987) and/or gram-negative sepsis (Kruger et al, 1991). This property makes the CD 14 receptor on monocytes an excellent marker for immune competence. A study conducted by Spagnoli et al, (1993) supports this contention.

While most post injury studies have demonstrated a decrease in monocyte membrane-bound CD14 as a result of

mitogen stimulated receptor shedding into the serum (Kruger et al, 1991; Volk et al, 1993; Rabin et al, 1993), Spagnoli et al (1993) revealed an early elevation in membrane-bound CD 14 after injury. In a study of 6 multiple trauma victims, with an ISS score of 20 or greater, membrane-bound CD 14 was measured one day after injury. The percentage of mean CD 14 positive monocytes demonstrated by trauma subjects (44% ± 10) revealed a more than two-fold increase when compared to age and sex matched, healthy normals (18.2% ± 4) (Spagnoli et al, 1993). The authors fail to report later CD 14 values and/or to explain the underlying mechanisms for this early change.

For the purposes of this study, anti-CD 14 linked with TRI-COLOR™ immunofluorescent dye with an excitation wavelength of 488nm and a peak emission wavelength of 667nm, was used to identify CD 14 on monocytes. The negative isotype for CD 14 is IgG-1 (Caltag Laboratories, 1993).

Monoclonal antibody anti-CD 25 - recognizes an antigen that is the low-affinity interleukin-2 receptor (IL-2R). The antigen has a molecular weight of 58 kDa and is found

on the surfaces of mitogen-activated T and B lymphocytes. The antigen's density is increased on Concanavalin A and IL-2 activated lymphocytes of normal subjects (Teodorczyk-Injeyan et al, 1987).

Contradictory results have been reported in the literature regarding CD 25 expression following traumatic injury (Teodorczyk-Injeyan et al, 1987; Hoyt et al, 1988; Schluter et al, 1991). Two studies found an increase in CD 25 antigen expression after injury (Hoyt et al, 1988; Schluter et al, 1991), while a third study found a decrease (Teodorczyk-Injeyan et al, 1987).

An increase in CD 25 expression was noted by Hoyt et al (1988) in a study of 30 blunt trauma patients (within 4 hours after injury and again at Days 5-7 and 14), when compared to 30 healthy normals. This increase in mean CD 25 expression correlated with the incidence of sepsis when comparing septic trauma subjects (9 ± 1.7) to non-septic trauma patients (3 ± 1.2) and healthy normals (4 ± 1.3).

Similar results are reported in a study by Schulter et al (1991) of 10 severely burned patients (total body surface area burned = 25% to 72%) at Days 1 to 50. Mean CD

25 expression was increased for cells incubated 72 hours in either phytohemagglutinin (PHA) (7.32% ± 0.37 to 27.78% ± 3.72) or interleukin 2 (IL-2) (8.58% ± 1.07 to 35.46% ± 4.99) as compared to healthy control volunteers (PHA 8.04% ± 0.28; IL-2 4.39% ± 0.18).

Opposing results are reported by Teodorczyk-Injeyan et al (1987) who revealed a decrease in mean CD 25 expression in 19 severely burned patients (total body surface area burned = 5% to 90%) as compared to 12 healthy volunteers at Days 1, 10, 20, 30, and 40 post burn. Subjects' cells were incubated in Con A for 72 hours with or without addition of interleukin 2. Controls were incubated without mitogen. Results indicate that mean CD 25 expression for both surviving (17-68%) and non-surviving (19-62%) patients initially demonstrated an increase when compared to control subjects (18-51%) within the first 24 hours post burn. A dramatic drop in CD 25 expression was seen in both surviving (7-30%) and non-surviving subjects (0-6%) at 10, 20, 30 and 40 days post burn. It is unclear what underlying mechanisms are responsible for the difference in results found in this study versus the studies by Hoyt et al, 1988 and Schluter et al, 1991.

For the purposes of this study, the monoclonal antibody anti-CD25 conjugated with the immunofluorescent dye TRI-COLOR™ , with an excitation wavelength of 488nm and a peak emission wavelength of 667nm, was used to identify CD 25 on activated lymphocytes (Caltag Laboratories, 1993). The negative isotype for CD 25 is IgG-1 (Caltag Laboratories, 1993).

Negative isotype - The negative isotype is a monoclonal antibody which is generated to recognize irrelevant proteins not found on the leukocyte cell surface membrane to assess non-specific binding of the identical isotype for a monoclonal antibody of interest. This isotype is utilized as a negative control when establishing gating criteria during flow cytometry analysis, ensuring that any cells falling outside the negative gate are positive for the monoclonal antibody under consideration (i.e. anti-CD 11b) (Hudson and Hayes, 1989). For the purposes of this study, negative isotype Mouse IgG-1, supplied by Caltag Laboratories, was used for analysis.

TABLE 3. SUMMARY OF CELL PHENOTYPES AND MONOCLONAL ANTIBODIES

CD	Cell Types	Monoclonal Antibody/ Clone	Negative Isotype	Fluorescent Dye	Cell Function
CD 11b	Granulocyte Monocyte	Mouse Anti-human CD11b /CR3(Bear1)	Mouse IgG-1	FITC	Complement Cell Adhesion
CD 16	Granulocyte	Mouse Anti-human CD 16 /3G8	Mouse IgG-1	PE	Complement
CD 14	Monocyte	Mouse Anti-human CD 14 /MEM 18	Mouse IgG-1	TRI-COLOR™	Myeloid Cell Growth
CD 25	Lymphocyte	Mouse Anti-human CD 25 /CD25-3G10	Mouse IgG-1	TRI-COLOR™	Interleukin 2 Receptor

CD = Common Determinant

IgG = Immunoglobulin gamma

FITC= Fluorescein isothiocyanate (green)

PE = Phycoerythrin (orange)

TRI-COLOR™ = (violet)

Cell Stimulants

Four stimulants or mitogens were used to activate the cells under study to proliferate (Benjamini et al, 1988; Widman, 1989). These mitogens included: phorbol-12-myristate-13-acetate(PMA), concanavalin A (Con A), muramyl dipeptide (MDP) and f-met-leu-phe (FMLP), all proven

stimulants of the cells populations in question. These soluble stimuli are easy to employ, have been extensively studied and provide reliable cell response. In addition, the selected stimulant promote cell stimulation via different pathways. Phorbol-12-myristate-13-acetate (PMA) and N-Acetylmuramyl-L-anlanyl-D-isoglutamine (MDP) are known to act directly on the intracellular activation of protein kinase C to alter the target cell's messenger ribonucleic acid (mRNA). Concanavalin A (Con A) and N-Formyl-methionyl-leucl-phenylalnine (FMLP) promote cell stimulation indirectly via cell surface membrane receptors to increase intracellular cAMP (Sigal and Ron, 1994).

Phorbol-12-myristate-13-acetate (PMA) - is a phorbol ester and a member of a family of potent tumor promoters and cell mitogens. It directly stimulates the activation of protein kinase C, required for intracellular protein phosphorylation and thus alteration in the mRNA of the cell's activation gene (Abbas et al, 1991). For the purposes of this study, PMA (Sigma Chemicals) was used in a 0.01µg/µl concentration after reconstitution with DMSO.

Concanavalin A (Con A) - is one of the most widely used and best characterized lectins. It binds with a

variety of sugar structures present on cell surfaces, especially mannose/glucose binding sites found on lymphocytes. While the mechanisms are not completely clear, the binding of Con A with these cell surface sugar binding sites results in significant increases in cyclic GMP and AMP, lymphocyte activation, increased blast formation and cell proliferation. Succinylated Con A (derivative of the natural lectin) is strongly mitogenic at doses ranging from 10µg/ml to 250µg/ml (Pierce Industries, 1989). For the purposes of this study, a 0.1µg/µl concentration (100µl) of succinylated Con A (Pierce Industries), reconstituted with distilled water, was used to stimulate lymphocytes.

N-Acetylmuramyl-L-anlanyl-D-isoglutamine (MDP) - or adjuvant peptide is a member of a family of low molecular weight glycopeptides (muramyl dipeptides) that are synthetic analogs of bacterial peptidoglycan fragments (found in bacteria cell walls). While the exact mechanism of action are unknown, its effects can be attributed to its ability to activate T-cell/macrophage interaction and increase IL-1 production. Known for its widely immunomodulating activities, including pyrogenic and pro-

inflammatory activities, it also is shown to be a potent mitogen for T and B lymphocytes, monocytes and granulocytes (Riveau et al, 1991). For the purposes of this study, MDP supplied by Sigma Chemicals and reconstituted with distilled water to a concentration of 0.1 µg/µl was used for cell stimulation.

N-Formyl-methionyl-leucl-phenylalnine (FMLP) - a chemotatic peptide well known for its activation of neutrophils an monocytes, FMLP has been shown to cause the up-regulation of C3b and iC3b receptors on neutrophil cell membranes and enhance the phagocytosis of both opsonized and unopsonized particles by neutrophils. It has also been associated with increased neutrophil superoxide release, polarization and degranulation along with increased chemotaxtic activity (Ogle et al, 1990, 1992). For the purposes of this study, FMLP supplied by Sigma Chemical and reconstituted with distilled water to a concentration 0.1 µg/µl was used as a cell stimulant.

Reagents

OptiLyse™ B Lysing Solution - A commercially prepared buffered solution containing 3.4% formaldehyde, OptiLyse™

(Amac, Inc.) was used to prepare subject's cells for phenotyping. OptiLyse™ contains no sodium azide and is not light-sensitive. This solution causes lysis of red blood cells and fixation of leukocytes without washing or centrifugation. It results in a leukocyte suspension free of red blood cells and suitable for flow cytometry.

0.15 M Phosphate buffered saline (PBS) - a buffer solution with a pH of 7.2 provided by Sigma Chemicals and comprised of sodium chloride (8.00 G/L), potassium chloride (0.20 G/L), 0.008 disodium hydrogen phosphate (1.5 G/L) and potassium dihydrogen phosphate (0.20 G/L) (Hudson and Hay, 1989). The above chemicals were dissolved in 1000 ml of distilled water and sterlized by adding 20 nM of sodium azide. The solution was then filtered by a double glass distillation process.

Cell Phenotyping Protocol

Subjects' blood was collected in a 7cc heparinized tube and placed immediately on ice and remained iced until ready for processing, within 2 hours.

Blood samples were processed for cell phenotyping (see Table 4) as follows:

1. Place 100 microliters of whole blood in (40) 12 X 75mm tubes.
2. Add 200 microliters of phosphate buffered saline (PBS) to each tube.
3. Add 100 microliters of stimulant as follows:
   - Tubes: 1-3, 12, 21-23, 32 - PBS.
   - Tubes: 4-5, 13-14, 24-25, 33-34 - Phorbol 12-myristate, 15-acetate (PMA) 0.01µg/µl.
   - Tubes: 6-7, 15-16, 26-27, 35-36 - Muramyl dipeptide (MDP) 0.1µg/µl.
   - Tubes: 8-9, 17-18, 28-29, 37-38 - Concanavalin A (ConA) 0.1µg/µl.
   - Tubes: 10-11, 19-20, 30-31, 39-40 - F-met-leu-phe (FMLP) 0.1µg/µl.
4. Vortex all tubes 2 - 3 seconds.
5. Incubate in heating blocks as follows:
   - Tubes: 1-2, 21-22 - 0 Degrees x 15 minutes
   - Tubes: 3-11, 23-31 - 37 Degrees x 15 minutes
   - Tubes: 12-20, 32-40 - 37 Degrees x 60 minutes
6. Upon removal from incubation, add 100 microliters of Optilyse™ solution (Amac, Inc.) to each tube.
7. Vortex all tubes 2 - 3 seconds.
8. Incubate all tubes at room temperature (18-25 Degrees) for 10 minutes.
9. During room temperature incubation add monoclonal antibodies (10 µl each) as follows:
   - Tubes: 1 and 21 - IgG-1 (Negative isotype control).
   - Tubes: 2 - 20 - CD 11b FITC/16 PE/14 TRICOLOR™.
   - Tubes: 22 - 40 - CD 25 TRICOLOR™.
10. Vortex 2 - 3 seconds.
11. Add 1 ml. deionized water to each tube, vortex and allow to sit for 10 minutes prior to analysis by flow cytometry. Specimens may be held for analysis for 24 hours at 0 Degrees.

TABLE 4. CELL PHENOTYPE PREPARATION PROTOCOL

	Whole Blood 100µl	PBS 200 µl	Stimulant 100µl	Incubate	Optilyse 100µl	Incubate	mAB 10µl	H_2O 1 cc
1	+	+	PBS	4°, 15	+	25°, 10	IgG-1	+
2	+	+	PBS	4°, 15	+	25°, 10	11bF 16P 14T	+
3	+	+	PBS	37°, 15	+	25°, 10	+	+
4	+	+	PMA	37°, 15	+	25°, 10	+	+
5	+	+	PMA	37°, 15	+	25°, 10	+	+
6	+	+	MDP	37°, 15	+	25°, 10	+	+
7	+	+	MDP	37°, 15	+	25°, 10	+	+
8	+	+	Con A	37°, 15	+	25°, 10	+	+
9	+	+	Con A	37°, 15	+	25°, 10	+	+
10	+	+	FMLP	37°, 15	+	25°, 10	+	+
11	+	+	FMLP	37°, 15	+	25°, 10	+	+
12	+	+	PBS	37°, 60	+	25°, 10	+	+
13	+	+	PMA	37°, 60	+	25°, 10	+	+
14	+	+	PMA	37°, 60	+	25°, 10	+	+
15	+	+	MDP	37°, 60	+	25°, 10	+	+
16	+	+	MDP	37°, 60	+	25°, 10	+	+
17	+	+	Con A	37°, 60	+	25°, 10	+	+
18	+	+	Con A	37°, 60	+	25°, 10	+	+
19	+	+	FMLP	37°, 60	+	25°, 10	+	+
20	+	+	FMLP	37°, 60	+	25°, 10	+	+

Repeat entire procedure for tubes 21-40 using mAB anti-CD 25T only

FITC= Fluorescein isothiocyanate (green)

PE = Phycoerythrin (orange)

TRI-COLOR™ = (violet)

Upon completion of specimen preparation, cell phenotyping was conducted on the Becton-Dickenson FACSCAN™ continuous flow cytometry using the Apple™-based computer software package, Cell Quest™. This program allows acquisition of a variety of cell populations in minutes, which can then be "gated" to electronically isolate specific populations for closer study. Utilizing this technique, histograms were generated to represent the mean fluorescence of CD marker (CD 11B, 16, 14, 25) expression on each selected cell population (lymphocytes, monocytes, granulocytes). The mean fluorescence for each experimental condition (e.g. CD 11b monocyte stimulation with PMA, CON A, MDP and FMLP at 15 and 60 minutes) was then compared to it's baseline unstimulated control and a ratio (stimulated cells/baseline cells) was created, in order to normalize the data.

Interpretation of Immunologic Data

Upon stimulation of each subject's granulocytes, monocytes and lymphocytes the mean fluorescence of their respective cell surface receptors was determined utilizing cell flow cytometry techniques. A mean fluorescence ratio was calculated by comparing each stimulated cell's mean

fluorescence to its own baseline unstimulated mean fluorescence.

When interpreting the immune status data a mean fluorescence ratio greater than 1.00 is considered an increase in mean fluorescence (increased immune responsiveness), while a mean value less than 1.0 is interpreted as a decrease in mean fluorescence (decreased immune responsiveness).

The mean fluorescence ratio results from the normal, healthy volunteers was then compared to the mean fluorescence ratio results of the 10 trauma subjects using an unpaired Willcoxon's T-Test. Discussion of these results follows in Chapter 4.

Study Procedure

Upon identification of potential study subjects from the trauma service daily census, patient charts were reviewed and the nursing staff consulted regarding selected patients' appropriateness for study inclusion based on inclusion/ exclusion criteria. Selected patients were then contacted and the purpose of the study, it's protocol, and risks/benefits were explained. Written consent was then obtained and patient's were assessed for cognitive function

using the Rancho Los Amigos Level of Cognitive Functioning Scale (CFS) (Appendix B).

In accordance with the Study Timeline (Appendix A), within 48 hours post injury, between 3:00 and 5:00 PM, the first data collection point was initiated. The candida and tuberculin skin tests were placed on the subject's forearm and the Stress/Arousal Check List (Appendix B) and Wallhagen's Experience of Current Situation Subscale (Appendix B) were read aloud to subjects and responses recorded accordingly. Subjects were also allowed to view an enlarged, easy-to-read version of the Likert response scales for each tool while questions were being asked.

Upon completion of the subjective tools, blood specimens were collected. Using a sterile Vacutainer and needle, a 5 cc red top tube (serum cortisol) and 7cc lavender top tube (cell phenotyping) were used to collect the required blood. Collected samples were immediately placed on ice and transported to the laboratory for analysis (serum cortisol to Department of Laboratory Medicine at San Francisco General Hospital and cell phenotyping specimen to study laboratory for analysis by principal investigator as described above).

At 48 hours post placement, the skin tests were evaluated. If the subject demonstrated a positive PPD and /or if there was no response to the candida antigen, he/she were excluded from the study because of the potential for prior immunosuppression.

At 96 hours post injury, between 3:00 and 5:00 PM, the second data collection point was instituted with a reassessment of cognitive function, repeat administration of the Stress/Arousal Check List and Wallhagen's Experience of Current Situation Subscale tools and redrawing of blood samples for serum cortisol and cell phenotyping. Subjects were also asked to complete the Demographic Data Sheet (Appendix C). A final chart review was done to collect other necessary clinical data and the subject's APACHE score was computed (Appendix B).

Power Calculation

The power of the proposed analysis to detect a difference in the dependent variable immune status over time, based on a medium effect size (f=.30) and Type I error rate .05 was .80 (Cohen, 1988). This power calculation was based on a sample population of 90.

Data Analysis

Demographic data were analyzed with descriptive statistics including means; standard deviations; medians and ranges for each independent and dependent variable across the two data points. In order to determine statistically significant differences in variables between the two data collection points paired t-tests were conducted. Inferential statistics were obtained by conducting Pearson's Correlation for each research question posed using the CRUNCH 4 PC statistical program. Each study question was statistically analyzed using a two-tailed alpha of $p < 0.05$ as indicative of statistical significance.

CHAPTER IV

RESULTS

This study examined the relationships among perceived control, stress response and immune response following traumatic injury. The relationships among study variables were also investigated for change over time, at early (48 hours) and late (96 hours) post injury or Time 1 and Time 2, respectively.

Descriptive Data

Sample Characteristics

Age/Sex - The sample of seven men and three women had a mean age of 37.6 years (± 16.6), with an age range of 19 to 77 years (Table 5).

Mechanism of Injury - Mechanism of injury analysis revealed that three subjects (30% of sample) sustained their injuries as the result of a fall, while two (20%) were involved in motorcycle accidents and one (10%) in a motor vehicle accident. Two subjects (20%) were the victims of automobile vs. pedestrian accidents, while the remaining two subjects (20%) were victims of violent crime and either shot or stabbed.

Diagnosis - Multiple or large bone fractures were the primary diagnoses for 5 subjects (50% of sample), while the

remaining subjects (50%) suffered a variety of lacerations to arteries and vital organs. One subject also presented with a primary diagnosis of pneumothorax.

Injury Severity - An Injury Severity Score (ISS) mean of 15.9 (± 8.4) and a range of 9 to 34 were noted (scale range 1 to 75), while APACHE scores ranged from 1 to 11 (scale 1 to 72), with a mean score of 5.8, ± 3.19.

Complications - Post-injury complications were assessed upon discharge/transfer of subjects. Three subjects (30% of sample) demonstrated no obvious complications following their traumatic injuries, while two (20%) displayed exacerbation of their pre-existing asthma condition. Five subjects (50%) demonstrated an episode of shock (BP < 90mm for 15 minutes or longer) secondary to blood loss.

Days in ICU - Days in ICU indicated that the study sample had a mean stay of 2.1 days, ± 1.8 and a range of 0 to 4 days. Three subjects (30% of sample) had no ICU days. Of the remaining subjects, four subjects (40%) stayed in the ICU 4 days, while two subjects (20%) experienced a one day ICU stay.

Length of Stay - Length of stay revealed an average mean stay of 7.9 days, ± 3.10 and a range of 4 to 14 days for the study population. Three subjects (30% of sample) were hospitalized for 10 days, while varying hospital stays of 4,5,6,7,8 and 14 days were demonstrated by the remaining

seven subjects (70%).

Disposition - Final disposition indicated that eight subjects (80%) were discharged home, one subject (10%) was sent to a long-term care facility and one subject (10%) was transferred to another acute care facility. No deaths occurred in the subject population.

TABLE 5. SAMPLE CHARACTERISTICS

SUBJECT AGE/SEX	MECHANISM OF INJURY	DIAGNOSIS	ISS	APACHE SCORE	POST-INJURY COMPLICATIONS	DAYS IN ICU	LENGTH OF STAY (Days)	FINAL DISPOSITION
1. 77F	Fall	Multiple Fractures	12	11	Asthma Exacerbation	0	10	Discharged
2. 52F	Fall	Fractured Femur	12	7	None	0	10	Long-term Care
3. 19M	Fall	Multiple Fractures	11	8	Asthma Exacerbation	4	10	Discharged
4. 43M	Motorcycle	Multiple Fractures	9	10	None	4	4	Transferred
5. 28M	Motorcycle	Fractures/ Pneumothorax	22	3	None	4	6	Discharged
6. 28F	MVA	Liver Lacerations	25	3	Shock*/Blood Loss	3	8	Discharged
7. 35F	Auto/Ped	Artery Lacerations	9	4	Shock/Blood Loss	0	14	Discharged
8. 30M	Auto/Ped	Degloving Inj. Artery Lacer.	9	6	Shock/Blood Loss	1	7	Discharged
9. 37M	GSW	Multiple Colon Lacerations	16	4	Shock/Blood Loss	1	5	Discharged
10 .27M	Stab Wound	Abdominal Evisceration	34	4	Shock/Blood Loss	4	5	Discharged

MVA = Motor Vehicle Accident
Auto/Ped = Automobile vs. Pedestrian
GSW = Gunshot Wound
*Shock - BP <90mm for 15 minutes or longer

Sample Demographics

Marital Status and Ethnicity - Sample demographics (Table 6) revealed that none of the subjects were married, seven subjects were single (70% of sample), one was separated (10%) and two were widowed (20%). Eight of the subjects (80%) were White, while two were Hispanic (20%). No African-Americans or Asians were represented in the sample population.

In an effort to identify pre-existing conditions or previous experiences which might influence the subject's stress response and/or immunity, a chart review was done and subjects were questioned regarding their previous hospitalizations, occurrence of injuries and prior health status.

Previous Hospitalization - Previous hospital stays lasting more than 24 hours were reported by six of the subjects (60% of sample), with five subjects (50%) reporting 1 to 3 previous hospitalizations and one subject (10%) reporting more than 3 previous hospitalizations. Four subjects (40%) denied any prior hospitalizations lasting more than 24 hour.

Prior Health Conditions - Five subjects (50% of sample) reported no prior health conditions or chronic diseases. Two subjects (20%) indicated a prior history of asthma, while one subject (10%) related a history of osteoporosis and another (10%) indicated previous episodes

of pulmonary embolus. Finally, one subject (10%) indicated a history of alcohol abuse and previous head injury.

Prior Injury - A history of prior injuries requiring hospitalization for more than 24 hours were also recorded for each subject. Three subjects (30% of sample) indicated they had 1 to 3 prior injuries, while the remaining seven subjects (70%) denied any previous hospitalizations for injury.

Prior Health Status - Subjects were asked to assess their health status prior to injury and rate it as: *Excellent, Good, Fair, Poor or Very Poor.* Four subjects (40% of sample) reported their prior health status to be excellent, while five (50%) claimed good health prior to their injury. Only one subject (10%) indicated his prior health status to be fair.

Delayed Hypersensitivity Response - Subjects' immunological response to the delayed hypersensitivity skin tests (done to determine immune status prior to injury) revealed that nine subjects (90% of sample) demonstrated a Mumps skin test wheal of 2mm or larger (wheal > 2mm = positive result), suggesting an adequate prior immune status. One subject (10%) displayed a Mumps skin test of approximately 1mm, suggesting a less than optimal prior immune status.

TB/HIV Exposure - All subjects (100% of sample) tested negative for prior TB exposure and denied any known

exposure to TB risks in the previous six months. All subjects denied a positive HIV status or high risk behaviors (e.g. intravenous drug abuse, unprotected intercourse, multiple partners).

Alcohol or Drugs on Arrival - Analysis of subjects for the presence of alcohol or drugs on arrival to the Emergency Department indicated that five subjects (50%) had detectable levels of alcohol or drugs or acknowledged alcohol/drug use upon arrival. The remaining five subjects (50%) denied alcohol/drug use and/or had no detectable levels in their admission alcohol/drug blood screens.

TABLE 6. SAMPLE DEMOGRAPHICS

SUBJECT AGE /SEX	MARITAL STATUS	ETHNIC BACK-GROUND	REPORTED PREVIOUS HOSPITAL STAY	REPORTED PREVIOUS INJURY	REPORTED PRIOR HEALTH CONDITIONS	REPORTED PRIOR HEALTH STATUS	DELAYED HYPER-SENSITIVITY RESULTS MUMPS/TB	TB/ HIV	ETOH/DRUG ON ARRIVAL
1. 77F	Widowed	White	>3	1-3	Asthma	Good	3mm/0mm	No	No
2. 52F	Widowed	Hispanic	1-3	1-3	Osteoporosis	Good	2mm/0mm	No	No
3. 19M	Single	White	0	0	Asthma	Excellent	2mm/0mm	No	No
4. 43M	Single	White	1-3	0	Pulmonary Embolus	Fair	2mm/0mm	No	No
5. 28M	Single	White	1-3	1-3	ETOH Abuse Head Injury	Good	2mm/0mm	No	Yes
6. 28F	Single	White	0	0	None	Good	3mm/0mm	No	No
7. 35F	Single	Hispanic	0	0	None	Excellent	2mm/0mm	No	Yes
8. 30M	Separated	White	0	0	None	Excellent	2mm/0mm	No	Yes
9. 37M	Single	White	1-3	0	None	Good	1mm/0mm	No	Yes
10 .27M	Single	White	1-3	0	None	Excellent	2mm/0mm	No	Yes

Single = Never Married
Previous Hospital Stay = Previous hospitalization > 24 hours
Previous Injury = Prior injury requiring hospitalization > 24 hours

Independent Variables

Subjects' individual scores for each of the independent variables are included in Table 7. Descriptive mean data for each of the independent variables are included in Table 8, along with normative data obtained from the literature.

Serum Cortisol - Serum cortisol (CORT) a measure of the physiologic stress response, achieved a demonstrated mean of 20.6 µg/dL, ± 8.9 (Range of 9.8 - 34.0 µg/dL) (Time 1, early post injury) and 16.0 µg/dL, ± 5.3 (Range 9.0 - 24.8 µg/dL) (Time 2, late post injury). The normative range of serum cortisol is 5 - 13 µg/dL. These results indicate that the sample population's mean scores at both Time 1 and Time 2 exceeded the normal range of cortisol secretion. The sample population thus demonstrated an increased physiologic stress response as measured by serum cortisol.

Perceived Control - Perceived control (PC) with a potential score range of 13 to 52 points demonstrated means of 40.7, ± 7.8 (Range 29.0 - 50.0) (Time 1, early post injury) and 39.9, ± 8.9 (Range 25.0 - 51.0) (Time 2, late post injury). While PC decreased slightly at Time 2, the sample mean fell well within the higher end of the perceived control scale at both Time 1 and Time 2, indicating the sample experienced high levels of perceived control.

Stress/Arousal CheckList - Subjective stress as measured by the Stress/Arousal CheckList (SACL) with a potential score range of 0 to 10.0 and a reported normative mean of 1.7, ± 2.0 and demonstrated sample means of 4.1, ± 2.4 (Time 1, early post injury) and 4.6, ± 3.2 (Time 2, late post injury), with scores ranging from 0 - 8.0 (Time 1) and 0 - 10.0 (Time 2). The sample mean was well above the normative mean at both Time 1 and Time 2, suggesting moderate to high levels of subjective stress existed in the sample population at both data collection points.

Stress/Arousal CheckList Visual Analogue Scale - The Stress/Arousal CheckList Visual Analogue Scale (SACLVAS) with a normative mean of 4.5cm, ± 2.2 demonstrated sample means of 3.8cm, ± 2.5cm (Time 1, early post injury) and 3.9cm ± 2.7cm (Time 2, late post injury), with a range of 0.5cm - 8.0cm (Time 1) and 0.1cm - 8.4cm (Time 2). The results of the SACLVAS suggest the sample population was experiencing a level of subjective stress well below the normative means and contradicts the findings of increased subjective stress suggested by the Stress/Arousal CheckList scale (SACL).

TABLE 7. SUBJECTS' INDIVIDUAL SCORES FOR INDEPENDENT VARIABLES

SUBJECT	SERUM CORTISOL (μg/dL)		PERCEIVED CONTROL		STRESS/ AROUSAL CHECKLIST		STRESS/ AROUSAL V.A.S.*	
DATA POINT	1	2	1	2	1	2	1	2
1	28.9	21.9	39	44	4.0	2.0	2.8	0.1
2	13.6	14.7	48	51	5.0	3.0	1.5	1.5
3	13.6	24.8	33	40	5.0	6.0	8.0	6.0
4	26.5	R	47	43	8.0	6.0	3.5	3.0
5	15.6	10.6	46	35	3.0	10.0	5.7	5.4
6	34.4	16.8	32	25	7.0	7.0	7.4	6.4
7	9.8	9.0	47	26	4.0	7.0	0.5	8.4
8	8.6	R	29	25	4.0	5.0	3.8	4.7
9	10.7	15.3	50	50	1.0	1.0	3.2	1.2
10	30.3	15.3	46	42	1.0	2.0	2.0	1.8

R = PATIENT REFUSED BLOOD DRAW
* VISUAL ANALOGUE SCALE

TABLE 8. SAMPLE'S MEAN SCORES FOR INDEPENDENT VARIABLES AND THEIR NORMATIVE DATA

	SERUM CORTISOL (μg/dL)		PERCEIVED* CONTROL		STRESS/ AROUSAL CHECKLIST		STRESS/ AROUSAL V.A.S.**	
TIME	1	2	1	2	1	2	1	2
SUBJECT DATA								
MEAN	20.6	16.0	40.7	39.9	4.1	4.6	3.8cm	3.9cm
SD	8.9	5.3	7.8	8.9	2.4	3.2	2.5cm	2.7cm
RANGE	9.8-34.0	9.0-24.8	29.0-50.0	25.0-51.0	0.0-8.0	0.0-10.0	0.5-8.0cm	0.1-8.4cm
NORMATIVE DATA								
MEANS					1.7		4.5cm	
SD					2.0		2.2cm	
RANGE	5.0 - 13.0		13 - 52					

*MEASURED BY WALLHAGEN'S EXPERIENCE OF CURRENT SITUATION SUBSCALE
**V.A.S. = VISUAL ANALOGUE SCALE - AT BOTTOM OF STRESS/AROUSAL CHECKLIST SCALE

Stressors of Hospitalization

The influence of narcotics, antibiotic NSAIDS (non-steroid anti-inflammatory drugs), receiving numerous blood transfusions and the occurrence of stress-producing invasive procedures (i.e. endotracheal intubation, placement of central lines/chest tubes, intraoperative procedures, etc.) have all been shown to alter serum cortisol (Pagana & Pagana, 1982). Occurrence of these variables were noted during data collection (Table 9).

Narcotics Given - Frequent narcotic use has been shown to suppress serum cortisol secretion (Pagana & Pagana, 1982). Analysis of the number of narcotics given revealed that at Time 1, one subject (10% of sample) received no narcotics, three (30%) received 1-3 narcotics and six (60%) were given 4 or more narcotics in the 24 hours immediately preceding data collection. Time 2 results reveal that three subjects (30%) required no narcotics, four subjects (40%) were given 1-3 narcotics and three subjects (30%) received 4 or more narcotics in the 24 hours immediately preceding data collection.

Antibiotics Given - Administration of certain antibiotics (e.g. cloxacillin) has been associated with a false elevation in serum cortisol levels (Pagana & Pagana, 1982). Analysis of the types and number of antibiotics given in the 24 hours immediately preceding data collection reveal that while no antibiotics associate with false elevations in serum cortisol were given, at Time 1 three

subjects (30% of sample) received no antibiotics, six subjects (60%) received 1-3 antibiotics and one subject (10%) was given 4 or more doses of antibiotics. At Time 2 five subjects (50%)received no antibiotics, four subjects (40%) were given 1-3 antibiotics and one subject (10%) received 4 or more antibiotics.

NSAIDS Given - Like narcotics, NSAIDS have been demonstrated to suppress serum cortisol levels (Pagana & Pagana, 1982). Assessment of the number of NSAIDS given reveals that at Time 1 none of the subjects were given NSAIDS in the 24 hours immediately preceding data collection. At Time 2 nine subjects (90% of sample) required no NSAIDS, while one subject (10%) was given 1-3 NSAIDS in the 24 hours immediately preceding data collection.

Procedures Done - Invasive procedures that could further elevate subjects' stress response were recorded in order to account for a potentially artificial elevation in serum cortisol. At Time 1 six subjects (60% of sample) had no procedures done in the 24 hours immediately preceding data collection, while four subjects (40%) had 1-3 procedures conducted. Seven subjects (70%) had no procedures conducted in the 24 hours immediately preceding Time 2 data collection, while three subjects (30%) had 1-3 procedures done.

Blood Transfusions Given - Receiving large numbers of blood transfusions after a traumatic injury have been

associated with immune function alteration (Chaudry et al, 1993). In the 24 hours preceding Time 1 data collection, seven subjects (70% of sample) received no blood transfusions, while two (20%) received 1-3 transfusions and one subject (10%) received 4 or more transfusions. In the 24 hours immediately preceding data collection at Time 2 none of the subjects received blood transfusions.

TABLE 9. POTENTIAL STRESSORS OF HOSPITALIZATION.

	NARCOTIC GIVEN		ANTIBIOTIC GIVEN		NSAID GIVEN		PROCEDURE DONE		BLOOD GIVEN	
DATA POINT / FREQUENCY	1	2	1	2	1	2	1	2	1	2
None	1*	3	3	5	10	9	6	7	7	10
1-3	3	4	6	4	0	1	4	3	2	0
>3	6	3	1	1	0	0	0	0	1	0

*NUMBER OF SUBJECTS RECEIVING THERAPEUTIC INTERVENTION

Immunologic Data Results

As discussed earlier in Chapter 3, under *Interpretation of Immunologic Data*, a mean fluorescence ratio (stimulated cell mean fluorescence/unstimulated cell baseline mean fluorescence) was generated for each of the ten trauma subjects and compared to the nine normal, healthy volunteers using an unpaired Willcoxon T-Test. The results of those comparisons were as follows:

CD 11B on Granulocytes - Analysis of results revealed no statistically significant difference between non-traumatized normal volunteers and post-trauma subjects when examining cell surface receptor mean fluorescence ratios for CD 11B on granulocytes (all stimulants after both 15 and 60 minute incubations) at both data collection points Time 1 (early post injury) and Time 2 (late post injury).

CD 11B on Monocytes - There were no significant differences between normals' and trauma subjects' CD 11B mean fluorescence response on monocytes for the majority of the stimulants used. There was a statistically significant difference between the mean fluorescence ratios of normals' (2.86, ± 0.44) and trauma subjects'(2.27, ± 0.65, p=0.04) of CD 11B monocytes stimulated by PMA at 15 minute incubation at Time 1. There was also a statistically significant difference between mean fluorescence ratios of normals' (1.51, ± 0.44) and trauma subjects' (0.79, ± 0.35, p=0.01) CD 11B response to PMA at 60 minute incubation at Time 1. Similar results were seen for the 60 minute incubation at Time 2 for normal subjects (1.51, ± 0.44) and trauma subjects (0.92, ± 0.63, p=0.04) All other stimulants failed to elicit a statistically significant response from CD 11B on monocytes.

CD 16 on Granulocytes - A lack of statistically significant response to the four stimulants at both 15 and 60 minute incubations was also revealed for CD 16 on granulocytes at both Time 1 and Time 2. Only PMA at the 15

minute incubation at Time 1 demonstrated a significant difference in mean fluorescence response for CD 16 on granulocytes between normals (1.13, ± 0.32) and trauma subjects (0.73, ± 0.26, p=0.01).

CD 14 on Monocytes - There was a statistically significant difference between trauma subjects and normals in response to all four stimulants at both 15 and 60 minute incubations for CD 14 on monocytes at both Time 1 and Time 2 (Tables 10 and 11).

Both normals and trauma subjects demonstrated an increase in CD 14 mean fluorescence after 15 minute incubation in response to all of the stimulants, but the trauma subjects' CD 14 mean fluorescence ratios displayed a consistently larger increase in mean fluorescence when compared to the normals' CD 14 monocyte values (Table 10).

Decreased responsiveness of CD 14 mean fluorescence was seen in normals after 60 minutes incubation in response to all of the stimulants, while trauma subjects continued to demonstrate an up-regulation of CD 14 mean fluorescence (Table 11).

TABLE 10. UNPAIRED T-TESTS - NORMALS VS TRAUMA SUBJECTS, (MEAN FLUORESCENCE/BASELINE RATIO) RESPONSE OF CD 14 RECEPTORS ON MONOCYTES TO FOUR STIMULANTS AT 15 MINUTE INCUBATION

	DATA POINT	GROUP/N	MEAN	DIFF.	D.F.	T	S.D.	p
STIMULUS/ TIME								
PMA/15	T-1	N/9	1.48	-0.61	17	-3.6	0.35	**0.01***
PMA/15	T-1	S/10	2.09		17		0.39	
PMA/15	T-2	N/9	1.48	-1.52	15	-2.5	0.35	**0.05***
PMA/15	T-2	S/8	3.10		15		2.20	
MDP/15	T-1	N/9	1.28	-0.52	17	-3.4	0.29	**0.01***
MDP/15	T-1	S/10	1.80		17		0.36	
MDP/15	T-2	N/9	1.28	-0.51	15	-4.1	0.29	**0.01***
MDP/15	T-2	S/8	1.79		15		0.21	
ConA/15	T-1	N/9	1.21	-0.29	17	-2.1	0.36	**0.05***
ConA/15	T-1	S/10	1.50		17		0.23	
ConA/15	T-2	N/9	1.21	-0.17	15	-1.1	0.36	0.30
ConA/15	T-2	S/8	1.38		15		0.27	
FMLP/15	T-1	N/9	1.11	-0.84	17	-3.7	0.24	**0.01***
FMLP/15	T-1	S/10	1.95		17		0.64	
FMLP/15	T-2	N/9	1.11	-0.86	15	-1.7	0.41	**0.01***
FMLP/15	T-2	S/8	2.52		15		0.41	

N = NORMALS
S = SUBJECTS
PMA = Phorbol-12-myristate-13-acetate
MDP = N-Acetylmuramyl-L-analnyl-D-isoglutamine
Con A = Concanavalin A
FMLP = N-Formyl-methionly-leucl-phenylalnine

TABLE 11. UNPAIRED T-TESTS - NORMALS VS TRAUMA SUBJECTS, (MEAN FLUORESCENCE/BASELINE RATIO) RESPONSE OF CD 14 RECEPTORS ON MONOCYTES TO FOUR STIMULANTS AT 60 MINUTE INCUBATION

	DATA POINT	GROUP/N	MEAN	DIFF.	D.F.	T	S.D.	p
STIMULUS/ TIME								
PMA/60	T-1	N/9	0.98	-0.67	17	-3.5	0.24	**0.01***
PMA/60	T-1	S/10	1.65		17		0.52	
PMA/60	T-2	N/9	0.98	-1.58	15	-2.1	0.24	**0.05***
PMA/60	T-2	S/8	2.55		15		2.25	
MDP/60	T-1	N/9	0.96	-0.74	17	-3.9	0.22	**0.01***
MDP/60	T-1	S/10	1.71		17		0.53	
MDP/60	T-2	N/9	0.96	-0.81	15	-7.4	0.22	**0.01***
MDP/60	T-2	S/8	1.77		15		0.23	
ConA/60	T-1	N/9	0.97	-0.65	17	-3.7	0.37	**0.01***
ConA/60	T-1	S/10	1.62		17		0.40	
ConA/60	T-2	N/9	0.97	-0.40	15	-2.3	0.37	**0.01***
ConA/60	T-2	S/8	1.37		15		0.36	
FMLP/60	T-1	N/9	0.93	-0.88	17	-4.9	0.41	**0.01***
FMLP/60	T-1	S/10	1.80		17		0.41	
FMLP/60	T-2	N/9	0.93	-1.34	15	-2.5	0.41	**0.01***
FMLP/60	T-2	S/8	2.27		15		1.59	

N = NORMALS
S = SUBJECTS
PMA = Phorbol-12-myristate-13-acetate
MDP = N-Acetylmuramyl-L-analnyl-D-isoglutamine
Con A = Concanavalin A
FMLP = N-Formyl-methionly-leucl-phenylalnine

CD 25 on Lymphocytes - There was a statistically significant difference between normals and trauma subjects response to the four stimulants at 15 minute incubation for CD 25 on lymphocytes at both Time 1 and Time 2 (Table 12). PMA, Con A and FMLP all produced statistically significant differences between the normals' and trauma subjects' CD 25 response on lymphocytes, at both Time 1 and Time 2, while MDP produced statistically significant differences only at Time 2.

Trauma subjects' CD 25 mean fluorescence on lymphocytes after 60 minutes of incubation failed to demonstrate statistical significance when compared to normals' values at both Time 1 and Time 2.

All of the trauma subjects' mean fluorescence ratios decreased at both 15 and 60 minute incubations in response to stimulation, while non-injured normal subjects consistently demonstrated an increase or up-regulation in mean fluorescence in response to stimulation.

TABLE 12. UNPAIRED T-TESTS - NORMALS VS SUBJECTS, (MEAN FLUORESCENCE/BASELINE RATIO) RESPONSE OF CD 25 RECEPTORS ON LYMPHOCYTES TO FOUR STIMULANTS AT 15 MINUTE INCUBATION

	DATA POINT	GROUP/N	MEAN	DIFF.	D.F.	T	S.D.	p
STIMULUS/ TIME								
PMA/15	T-1	N/9	1.13	0.14	17	3.7	0.11	**0.01**
PMA/15	T-1	S/10	0.99		17		0.05	
PMA/15	T-2	N/9	1.13	0.14	15	3.7	0.11	**0.01**
PMA/15	T-2	S/8	0.99		15		0.05	
MDP/15	T-1	N/9	1.18	0.13	17	1.1	0.25	0.3
MDP/15	T-1	S/10	1.05		17		0.24	
MDP/15	T-2	N/9	1.18	0.24	15	2.5	0.25	**0.04**
MDP/15	T-2	S/8	0.94		15		0.12	
ConA/15	T-1	N/9	1.1	0.1	17	.85	0.12	**0.05**
ConA/15	T-1	S/10	1.0		17		0.19	
ConA/15	T-2	N/9	1.1	0.15	15	2.6	0.12	**0.02**
ConA/15	T-2	S/8	0.95		15		0.11	
FMLP/15	T-1	N/9	1.17	0.18	17	2.9	0.19	**0.01**
FMLP/15	T-1	S/10	0.99		17		0.06	
FMLP/15	T-2	N/9	1.17	0.27	15	3.2	0.19	**0.01**
FMLP/15	T-2	S/8	0.90		15		0.15	

N = NORMALS
S = SUBJECTS
PMA = Phorbol-12-myristate-13-acetate
MDP = N-Acetylmuramyl-L-analnyl-D-isoglutamine
Con A = Concanavalin A
FMLP = N-Formyl-methionly-leucl-phenylalnine

The consistent statistically significant difference seen between the normal subjects' and the trauma subjects' CD 14's mean fluorescence response on monocytes at both 15 and 60 minutes incubation and the response of CD 25 on lymphocytes at 15 minutes incubation provided a valid immune outcome measure for this study. Given the well-documented ability of PMA and Con A to consistently and reliably stimulate monocytes (Abbas, 1991; Baybutt & Holsboer, 1990; Ogle, 1990, 1992) and lymphocytes (Depper et al, 1984; Butcher et al, 1989), the mean fluorescence response of the cells to these stimulants was used as the final outcome measures of immunologic status of the study

Utilizing the mean fluorescence results of CD 14 on monocytes (at 15 and 60 minute incubations) and CD 25 on lymphocytes (at 15 minute incubation), correlations were done with these variables and each of the independent variables to answer the following questions regarding relationships between each of the variables.

Research Questions

Research Question 1

"Does a subject's: sense of perceived control; subjective stress response; physiologic stress response; and/or immune status change between Time 1 (48 hours, early post injury) and Time 2 (96 hours, late post injury)?"

In order to answer Question 1, a paired difference t-Test was conducted to identify differences between the variables at Time 1 (early post injury) and Time 2 (late post injury). The results are displayed in Table 13 below.

There was no statistically significant difference in the independent variables serum cortisol, subjective stress (Stress/Arousal CheckList - SACL & visual analogue scale - SACLVAS) and perceived control (PC) between Time 1 and Time 2 (Table 13).

Stress/Arousal CheckList (SACL) - There was a very slight increase in the Stress/Arousal CheckList mean score at Time 1 (4.11, ± 2.4) to Time 2 (4.61, ± 3.22). This change was not statistically significant.

Stress/Arousal Visual Analogue (SACLVAS) - The Stress/Arousal Visual Analogue Scale mean score at Time 1

(3.84, ± 2.47) also increased slightly at Time 2 (Mean 3.85, ± 2.72), but this change was not statistically significant.

Perceived Control - While there was a slight decrease in perceived control mean scores from Time 1 (40.70, ± 7.83) to Time 2 (39.90, ± 8.95), these results were not statistically significant.

Serum Cortisol - A decrease in mean serum cortisol from Time 1 (21.09, ± 9.0) to Time 2 (16.03, ± 5.3) also occurred. This change was not statistically significant.

TABLE 13. PAIRED T-TESTS, TIME 1 VS. TIME 2, MEAN SCORES OF INDEPENDENT VARIABLES

VARIABLE	DATA POINT	N	MEAN	DIFF.	SD	t	df	p
Cortisol	T-1	8	21.09	5.05	8.97	1.4	7	0.2
	T-2	8	16.03		5.27		6	0.9
Stress/ Arousal Scale	T-1	10	4.11	-0.50	2.40	-0.6	9	0.6
	T-2	10	4.61		3.22		8	0.1
Stress Visual Analogue	T-1	10	3.84	-0.10	2.47	-0.01	9	1.0
	T-2	10	3.85		2.72		8	0.3
Perceived Control**	T-1	10	40.70	0.80	7.83	0.3	9	0.8
	T-2	10	39.90		8.95		8	0.5

* SIGNIFICANT AT p <0.5
**MEASURED BY WALLHAGEN'S EXPERIENCE OF CURRENT SITUATION SUBSCALE
DIFF. = DIFFERENCE

A similar lack of statistical significance was noted when comparing the immune status variables CD 14 on monocytes (15 and 60 minute incubation) and CD 25 (15 minute incubation) from Time 1 (48 hours, early post injury) to the Time 2 (96 hours, late post injury) results (Table 14).

TABLE 14. PAIRED T-TESTS, TIME 1 VS. TIME 2, MEAN SCORES OF IMMUNE STATUS VARIABLES

VARIABLE	DATA POINT	N	MEAN	DIFFERENCE	SD	t	df	p
CD 14/Monocytes PMA/15	T-1	8	2.1	-0.65	0.38	-1.2	7	0.3
CD 14/Monocytes PMA/15	T-2	8	2.8		1.65		6	0.3
CD 14/Monocytes PMA/60	T-1	8	1.6	-1.0	0.3	-1.3	7	0.3
CD 14/Monocytes PMA/60	T-2	8	2.6		2.3		6	0.7
CD 14/Monocytes CON A/15	T-1	8	1.5	0.2	0.2	1.5	7	0.2
CD 14/Monocytes CON A/15	T-2	8	1.4		0.3		6	0.7
CD 14/Monocytes CON A/60	T-1	8	1.6	0.2	0.4	1.1	7	0.3
CD 14/Monocytes CON A/60	T-2	8	1.4		0.4		6	0.7
CD 25/Lymphocytes PMA/15	T-1	8	0.9	0.02	0.08	0.5	7	0.6
CD 25/Lymphocytes PMA/15	T-2	8	0.9		0.1		6	0.6
CD 25/Lymphocytes PMA/60	T-1	8	0.9	0.06	0.1	0.8	7	0.4
CD 25/Lymphocytes PMA/60	T-2	8	0.9		0.1		6	0.6
CD 25/Lymphocytes CON A/15	T-1	8	1.0	0.1	0.2	2.0	7	0.08
CD 25/Lymphocytes CON A/15	T-2	8	0.9		0.1		6	0.2
CD 25/Lymphocytes CON A/60	T-1	8	1.1	0.2	0.2	2.1	7	0.08
CD 25/Lymphocytes CON A/60	T-2	8	0.9		0.1		6	0.5

* SIGNIFICANT AT p <0.5

Given this consistent lack of statistical significance between Time 1 and Time 2 independent and dependent variables it was decided to consider only Time 1 (48 hours, early post injury) results for further analysis.

Research Question 2

"Does a subject's: sense of perceived control; subjective stress response (SACL, SACLVAS); and/or physiologic stress response (serum cortisol); demonstrate a statistically significant relationship with immune status as measured by the mean fluorescence of CD 14 on monocytes and CD 25 on lymphocytes (in response to PMA and CON A after 15 and 60 minute incubations)?" To answer this question Pearson's Correlations were conducted between each of the independent variables. Results of these correlation are in Table 15.

Correlation Between Independent Variables

Serum Cortisol - Despite an elevation in serum cortisol levels demonstrated by the study subjects, this variable failed to demonstrate a statistically significant correlation with any of the other independent variables. These results indicate that while increased subjective stress (SACL, SACLVAS) and physiologic stress (cortisol) was

documented in the study subjects there was no significant correlation between these variables.

Subjective Stress - The Stress/Arousal CheckList Scale (SACL) and the Stress/Arousal Visual Analogue Scale (SACLVAS) demonstrated a strong positive correlation ($r=0.84$, $p=0.01$) in accordance with similar results previously reported in the literature (King,). Despite the strong correlation between these two tools, one (SACL) indicated the study population was experiencing increased subjective stress, while the other tool (SACLVAS) indicated the population's stress was within a normal (low stress) range. These results confirm that the two scales are accurately measuring stress, but are probably looking at slightly different concepts or elements of stress.

Perceived Control - Pearson's correlation of the independent variables revealed that as hypothesized, perceived control negatively correlated with both measures of subjective stress; Stress/Arousal CheckList Scale ($r=-0.70$, $p=0.05$) and Stress/Arousal Visual Analogue Scale ($r=-0.77$, $p=0.03$) indicating that as perceived control increased the subjects' sense of subjective stress

decreased. Conversely as perceived control decreased, subjective stress increased.

TABLE 15. PEARSON'S CORRELATIONS OF INDEPENDENT VARIABLES

	SERUM CORTISOL	STRESS/AROUSAL SCALE	STRESS VISUAL ANALOGUE SCALE	PERCEIVED CONTROL
SERUM CORTISOL	1.00 0.00	-0.17 0.68	-0.08 0.84	-0.01 0.98
STRESS/AROUSAL SCALE		1.00 0.00	**0.84** **0.01***	**-0.70** **0.05***
STRESS VISUAL ANALOGUE SCALE			1.00 0.00	**-0.77** **0.03***
PERCEIVED CONTROL				1.00 0.00

CELL CONTENTS - PEARSON'S CORRELATION/p VALUE
* SIGNIFICANT AT $p < 0.05$

Correlation Between Independent Variables and Dependent Variables

The statistically significant Pearson's correlations between the independent variables and the dependent outcome variables are displayed on Figure 6 and in Table 16.

Stress/Arousal CheckList - Negative correlations were demonstrated between the Stress/Arousal CheckList Scale (SACL) and mean fluorescence of CD 14 on monocytes (stimulated by CON A following both 15 and 60 minute incubations). These results indicate that as subjective

stress increased the mean fluorescence of CD 14 on monocytes following CON A stimulation demonstrated decreased responsiveness (i.e. immunosuppression).

Stress/Arousal CheckList Visual Analogue Scale - Similar results were seen when the Stress/Arousal CheckList Visual Analogue Scale (SACLVAS) was correlated with the dependent variables. A negative correlation was seen between SACLVAS and mean fluorescence of CD 14 on monocytes stimulation by PMA ($r=-0.68$, $p=0.03$) and CON A ($r=-0.84$, $p=0.01$) following 60 minutes incubation. A negative correlation was also seen between SACLVAS and the mean fluorescence of CD 25 on lymphocytes in response to CON A after 60 minutes incubation ($r=-0.72$, $p=0.04$). These results indicate that as subjective stress increased, both mean fluorescence of CD 14 on monocytes and CD 25 on lymphocytes displayed decreased responsiveness (i.e. immunosuppression).

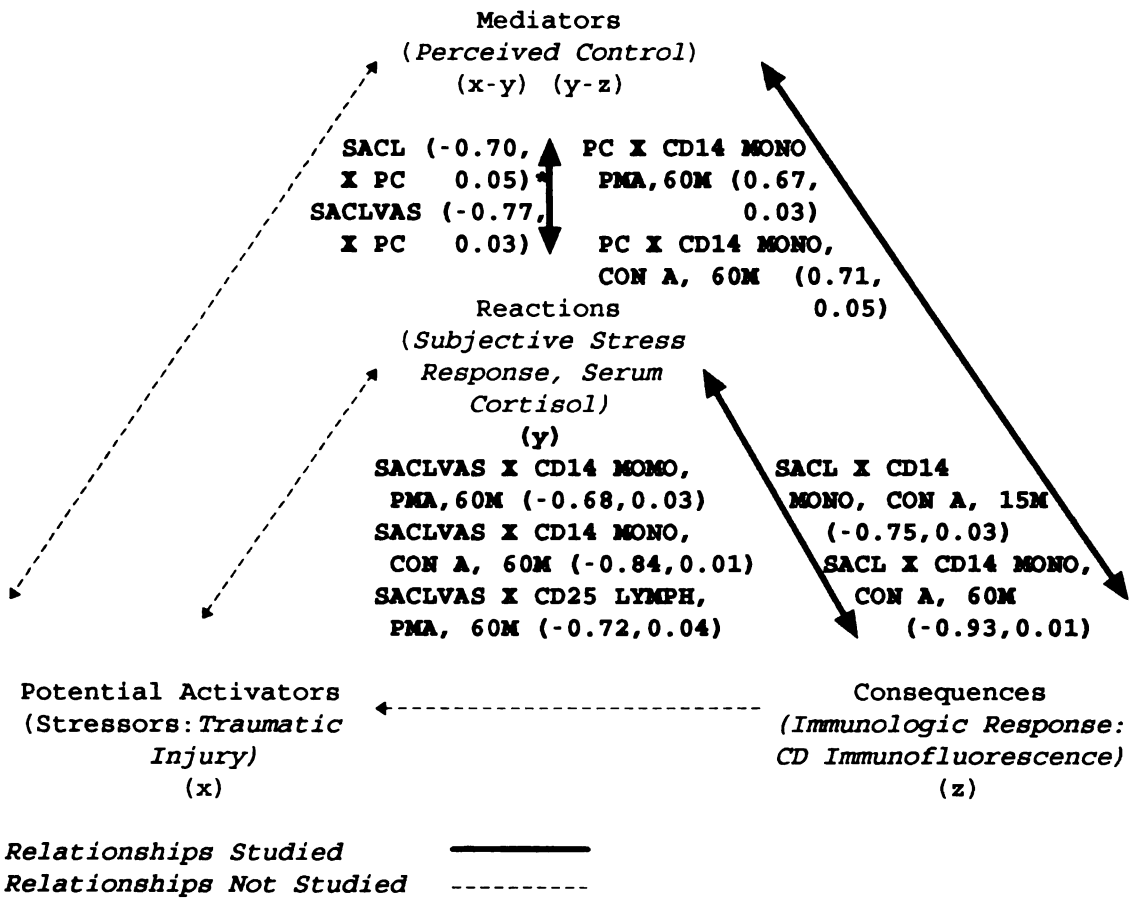
Perceived Control - Perceived control demonstrated a positive correlation with mean fluorescence of CD 14 on monocytes following stimulation by both PMA and CON A after 60 minute incubations. These results indicate that as perceived control increased, the mean fluorescence of CD 14

on monocytes demonstrated increased responsiveness (i.e. immunoenhancement).

Serum Cortisol - Serum cortisol failed to significantly correlate with either of the dependent variables (i.e. mean fluorescence of CD 14 on monocytes and CD 25 on lymphocytes stimulated by PMA and CON A after 15 and 60 minute incubations).

There were also no statistically significant correlations between serum cortisol, SACL, SACLVAS and perceived control and the mean fluorescence of CD 25 lymphocytes (following CON A stimulation after both 15 and 60 minutes of incubation.) Finally, there were no statistically significant correlations between the independent variables (serum cortisol, SACL, SACLVAS and perceived control) and mean fluorescence of CD 14 on monocytes following PMA and CON A stimulation and CD 25 on lymphocytes following PMA stimulation after 15 minutes of incubation.

Figure 6. CONCEPTUAL FRAMEWORK FOR STRESS RESPONSE, PERCEIVED CONTROL AND IMMUNITY FOLLOWING TRAUMATIC INJURY WITH STATISTICALLY SIGNIFICANT CORRELATIONS SUPERIMPOSED.



*(Pearson's Correlation Coefficient , p Value)
SACL = STRESS/AROUSAL CHECKLIST
SACLVAS = STRESS/AROUSAL CHECKLIST VISUAL ANALOGUE SCALE
PC = PERCEIVED CONTROL
MONO = MONOCYTES
LYMPH = LYMPHOCYTES
PMA = PHORBOL-12-MYISTATE-13-ACETATE
CON A = CONCANAVALIN A
M = MINUTES

NOTE: Adapted from: Elliott, G.R., Eisdorfer, C. (1982) *Stress and Human Health.* New York: Springer Publishing Company, p.19.

TABLE 16. PEARSON'S CORRELATION OF INDEPENDENT VARIABLES WITH DEPENDENT (IMMUNE STATUS) VARIABLES.

	SERUM CORTISOL	STRESS/AROUSAL SCALE	STRESS VISUAL ANALOGUE SCALE	PERCEIVED CONTROL
CD14/Monocytes	-0.38	0.66	0.34	-0.31
PMA/15	0.36	0.07	0.41	0.45
CD14/Monocytes	-0.42	-0.47	**-0.68**	**0.67**
PMA/60	0.23	0.17	**0.03***	**0.03***
CD14/Monocytes	-0.20	**-0.75**	-0.57	0.49
CON A/15	0.63	**0.03***	0.14	0.22
CD14/Monocytes	0.16	**-0.93**	**-0.84**	**0.71**
CON A/60	0.71	**0.01***	**0.01***	**0.05***
CD25/Lymphocytes	0.23	0.38	0.29	-0.09
PMA/15	0.52	0.28	0.41	0.81
CD25/Lymphocytes	-0.11	-0.47	**-0.72**	0.60
PMA/60	0.80	0.24	**0.04***	0.12
CD25/Lymphocytes	0.21	-0.04	-0.11	-0.39
CON A/15	0.60	0.97	0.77	0.26
CD25/Lymphocytes	0.07	-0.03	0.14	-0.51
CON A/60	0.84	0.93	0.69	0.13

CELL CONTENTS - PEARSON'S CORRELATION/p VALUE
* SIGNIFICANT AT p < 0.05

Research Question 3

"Do any of the demographic or potentially stressful variables related to hospitalization demonstrate a statistically significant relationship with the independent variables subjective stress, perceived control, serum cortisol and/or immune status (as demonstrated by the mean fluorescence of CD 14 on monocytes and CD 25 on lymphocytes

in response to PMA and CON A after 15 and 60 minute incubations)?" "Do any of the demographic or potentially stressful variables related to hospitalization demonstrate a significant relationship when correlated with each other?"

Correlations were conducted between Injury Severity Score (ISS), APACHE Score, Days In ICU, Number Of Narcotics Given, Number Of Antibiotics Given, Number of NSAIDS Given, Number Of Invasive Procedures Done, Number of Transfusions Given, Mumps Results, and White Blood Count (WBC) and each of the independent and dependent variables. The results of these correlations are contained in Table 17 below.

Injury Severity Score There was a statistically significant positive correlation between Injury Severity Score (ISS) and the number of transfusions given ($r=0.81$, $p=0.05$) indicating that as injury severity increased trauma subjects also received greater numbers of blood transfusions. No statistically significant correlations between ISS and the serum cortisol, subjective stress (SACL, SACLVAS), perceived control or the measures of immune response were noted.

APACHE Score In this sample of trauma subjects the APACHE Score, which is designed to reflect a subject's

physiologic status, was significantly and positively correlated with serum cortisol (r=0.88, p=0.02). These results indicate that as the subjects' physiologic scores increased (i.e. greater severity of illness) the level of serum cortisol (i.e. physiologic stress response) also increased. No statistically significant correlations were seen between the APACHE Score and the remaining independent or dependent variables.

Days In ICU The number of days subjects spent in the ICU was significantly correlated with both of the subjective stress variables, Stress/Arousal CheckList (r=0.80, p=0.05) and Stress/Arousal Visual Analogue Scale (r=0.79, p=0.05), indicating that subjective stress increased as subjects spent more time in the ICU.

Days in ICU was also significantly correlated with the immune response measures. When correlated with CD 14 on monocytes stimulated by CON A at 60 minute incubation there was a negative relationship (r=-0.84, p=0.03) indicating that as the number of days in ICU increased, there was less responsiveness of the mean fluorescence of the CD 14 receptors on monocytes (i.e. immunosuppression). Similarly, when correlated with CD 25 on lymphocytes stimulated by CON

A at 60 minute incubation a negative relationship (r=-0.84, p=0.03) resulted which indicated that as the number of days in ICU increased the mean fluorescence of CD 25 on lymphocytes demonstrated decreased responsiveness (i.e. immunosuppression).

Mumps Results The subjects' response to the mumps skin test demonstrated a statistically significant positive correlation with their serum cortisol levels (r=0.80, p=0.05). These results suggest that an increased reactivity to the mumps antigen (a measure of prior immune function) is related to an increase in serum cortisol (a measure of physiologic stress).

Number of Narcotics Given The number of narcotics given to subjects correlated significantly with CD 14 on monocytes stimulated by PMA at both 15 (r=-0.88, p=0.02) and 60 minute (r=-0.83, p=0.04) incubations. These results indicate that as subjects received more narcotics the mean fluorescence of CD 14 on monocytes demonstrated less responsiveness of the receptor. The number of narcotics given to subjects also strongly positively correlated with the number of antibiotics given (r=0.86, p=0.02).

Number of Antibiotics Given The number of antibiotics given to subjects demonstrated a statistically significant correlation with only one variable, the number of blood transfusions received (r=0.87, p=0.02).

Number of NSAIDS Given The number of NSAIDS (non-steroid anti-inflammatory drugs) given to subjects demonstrated a statistically significant positive correlation with CD 25 on lymphocytes mean fluorescence response to CON A after a 15 minute incubation (r=0.95, p=0.01). These results indicate that as NSAIDS usage increased the mean fluorescence of CD 25 on lymphocytes demonstrated decreased responsiveness of the receptor or immunosuppression.

Number of Invasive Procedures Done The number of invasive procedures done (e.g. surgery, central line placement, fixation of broken bones) demonstrated a strong correlation with immune status variables. A negative correlation occurred when number of procedures done was correlated with the mean fluorescence of CD 14 monocytes stimulated by CON A after 15 minute incubation (r=-0.88, p=0.02). These results indicate that as the number of procedures increased the mean fluorescence of CD 14 on

monocytes demonstrated decreased responsiveness or immunosuppression.

Similar results were seen when the number of procedures done was correlated with CD 25 on lymphocytes stimulated by PMA ($r=0.89$, $p=0.01$) and CON A ($r=0.89$, $p=0.01$) after 15 minute incubations. These results revealed that as the number of procedures done increased, CD 25 on lymphocytes became less responsive or immunosuppressed.

Whole Blood Count The whole blood count (WBC) demonstrated a statistically significant correlation with only one variable, mean fluorescence of CD 14 on monocytes in response to PMA after 15 minute incubation ($r=0.88$, $p=0.01$). These results indicate that as the WBC increased the mean fluorescence of CD 14 on monocytes also displayed more receptor responsiveness or immunoenhancement.

TABLE 17. SIGNIFICANT CORRELATIONS OF DEMOGRAPHIC VARIABLES AND POTENTIAL STRESSORS OF HOSPITALIZATION WITH INDEPENDENT/DEPENDENT VARIABLES

	ISS	APACHE	DAYS IN ICU	MUMPS RESULTS	NARCOTICS GIVEN	ANTIBIOTICS GIVEN	NSAIDS GIVEN	PROCEDURES DONE	WBC
STRESS/AROUSAL CHECKLIST			0.80 0.05						
STRESS VISUAL ANALOGUE SCALE			0.79 0.05						
SERUM		0.88		0.80					
CORTISOL		0.02		0.05					
CD14 MONOCYTES/ PMA/15					-0.88 0.02				0.88 0.01
CD14 MONOCYTES/ PMA/60					-0.83 0.04				
CD14 MONOCYTES/ CON A/15								-0.88 0.02	
CD14 MONOCYTES/ CON A/60			-0.84 0.03						
CD25 LYMPHOCYTE PMA/15								0.89 0.01	
CD25 LYMPHOCYTE CON A/15							0.95 0.01	0.89 0.01	
CD25 LYMPHOCYTE CON A/60			-0.84 0.03						
NARCOTICS GIVEN									
ANTIBIOTICS GIVEN					0.86 0.02				
TRANSFUSION GIVEN	0.81 0.05					0.87 0.02			
WBC							0.90 0.01		

CHAPTER V

DISCUSSION

The relationships among stress, perceived control and immunity are complex and multifaceted. The perception of control over a stressor appears to act as a potent mediator in the relationship between the stressor, its resultant stress response and long-term consequences. The literature consistently supports the hypothesis that increasing a subject's sense of control over aversive stimuli will ameliorate its negative impact and potentially debilitating aftermath. A strong sense of perceived control over a stressor has been credited with improving subjects' mood (Breier et al, 1987; Ferington, 1986), recovery from physical disability and surgery (Krantz, 1980; Partridge & Johnston, 1989); and coping with the effects of aging (Rodin & Langer, 1976, 1977; Avorn & Langer, 1982). Controllability has also been shown to consistently mediate the effect of stress on immunity in both animals (Sklar & Anisman, 1979; Visintainter et al, 1982; Laudenslager et al, 1983; Mormede et al, 1984, 1988; Ben-Eliyahu, 1991) and humans (Locke et al, 1984; Weisse, 1990; Wiedenfel, 1990;

Sieber et al, 1992). This study used a repeated measure design to investigate the relationships between stress response, perceived control and immunity following traumatic injury (a situation widely documented in the literature to be related to immune dysfunction).

Findings in Relation to the Hypotheses and Related Literature

This study investigated the relationships among perceived control, subjective and physiologic stress response and immune status following traumatic injury. It was hypothesized that subjects experiencing low perceived control over their traumatic injury and subsequent hospitalization would in turn demonstrate high levels of subjective and physiologic stress response which would correlate with an abnormal change in immune status. Conversely, a high level of perceived control would negatively correlate with a lower level of subjective and physiologic stress response and normal or enhanced immunity.

Serum Cortisol

The mean serum cortisol level of the study sample was elevated well above the normal range (5-13 µg/dL), as were the individual scores of seven subjects at Time 1 (mean 20.6 µg/dL) and six subjects at Time 2 (mean 16.0 µg/dL). This elevation failed to significantly correlate with any of the other study independent or dependent variables. This lack of significant correlation may have been a result of the small sample size at Time 1 (N=10), and Time 2 (N=8). The sample size of Time 2 was especially problematic, having been reduced to 8 from the original sample size of 10, as a result of the refusal by two subjects to allow a second blood draw. Increasing the sample size should be a major consideration for any future studies.

When examining the individual cortisol levels of each subject it was interesting to note that while cortisol levels above the norm were seen in five subjects at both Time 1 and Time 2, of this group, three subjects demonstrated a substantial decrease at Time 2. These results suggest that while the subjects were still experiencing increased physiologic stress, their stress

response had diminished. This drop may have been a result of the effects of habituation frequently seen with chronic stress (Keller et al; 1991). While the subjects may still have been responding to the continued stress of their environment, perhaps their pituitary-adrenal axis was beginning to be less responsive to the stimuli presented. These results underscore the need to time data collection to correspond with the most likely period of increased stress response.

Subjective Stress

Contradictory results were found when examining subjective stress in the sample population. Mean scores of 4.1 and 4.6 (normative mean 1.7) were demonstrated for the Stress/Arousal CheckList (SACL) and 3.8 and 3.9 (normative mean 4.5) for the Stress/Arousal CheckList Visual Analogue Scale (SACLVAS). The SACL results indicate the subjects were experiencing increased subjective stress, while the SACLVAS indicates subjective stress was well below the normative mean. While the SACL and SACLVAS results are contradictory, the correlation coefficient of 0.84 displayed between these two tools agrees with the correlation coefficient of 0.83 reported by King et al

(1987). These contradictory results could be the result of several factors: the small sample size which falsely skewed the results; subjects' attempt to appear less stressed, especially when asked to rate their stress level on a line scale; and flaws in the measurement tool.

The need to increase sample size has been discussed elsewhere and remains an important issue for this variable. A larger sample may have resulted in more congruent results.

Subjects' desire to appear less stressed then they were really feeling may have been a major factor in these contradictory results. A type of "Hawthorne effect" threat to external validity (Woods et al, 1988) may have occurred, the subjects may have been reacting to the experience of being studied and not wanting to appear weak or unable to handle stress. This effect was especially evident when the tool was administered while subject's friends or family were present. Two subjects were studied under these conditions and each time the subject was observed to be looking at the friend or relative prior to answering each question. During subsequent testing (Time 2), friends and family were asked to leave the room until the subject was finished. Higher

stress scores were demonstrated when subjects were tested without family of friends as witnesses.

Male subjects also appeared to have difficulty admitting or acknowledging increased stress. Three male subjects were very forceful in their denial of feelings of stress and showed almost identically low scores on both the subjective SACL and the SACLVAS at both Time 1 and Time 2, while demonstrating serum cortisol levels well above the normative value.

Flaws in the tool itself may have posed a problem. The SACL's 4-point Likert response scale (e.g. *Definitely Yes, Slightly Yes, Not Sure/Don't Understand, Definitely Not)* may have been difficult for subjects to understand and respond to accurately. The response *Not Sure/Don't Understand* appeared to confused subjects and failed to give them an option to indicate a somewhat negative response. Normally a Likert scale would have allowed a *Slightly Negative* response instead of the *Not Sure/Don't Understand* response (Wood et al, 1988). King et al (1987) fails to address the reason behind the wording of this response and reports an alpha coefficient of 0.93 for this tool. Despite King's assertion it would appear the wording of this response poses a threat

to the validity of this instrument and may explain some of the conflicting study results.

Finally, it would appear that the two tools, SACL and SACLVAS, while both measuring subjective stress response, may tap different elements or aspects of the stress concept. This would explain the contradictory results and the high correlation coefficient.

Perceived Control

The relatively high level of perceived control demonstrated by the study subjects was an unexpected finding given the highly uncontrollable nature of their injury situation. Each subject had been the victim of either a violent crime or an unexpected accident and had been placed in a situation of high stress, low predictability and uncertain outcome. Yet the mean perceived control score (40.7 Time 1; 39.9 Time 2, normal range 13 - 52) indicated these subjects were experiencing a strong sense of control.

The literature identifies a variety of factors that can influence a subject's sense of control. Some of these factors include: illusion of control; attributions of causation; predictability; and preference for control.

Attributions of Causation - In the past, the individual's underlying locus of control has been hypothesized to be central to perceptions of control over all possible outcomes. This has not been supported by the literature which demonstrates that the nature of the outcome itself appears to have a greater impact on the sense of perceived control. It has been illustrated that positive outcome events are related to greater perceptions of control than events with negative outcomes (e.g. rape victim who helps convict her rapist vs. a victim who refuses to testify) (Wallston et al, 1987).

Subjects in the current study frequently provided spontaneous insight into their experiences and feelings. A number of the study subjects (5) who demonstrated higher levels of perceived control, also verbalized feelings of relief and thankfulness that their injuries and subsequent outcomes had not been worse then they were. Several subjects (4) indicated that while their experience had been traumatic both physically and emotionally, they felt God or some other powerful force had been watching out for them. Several subjects (6) indicated their experiences had given them a new appreciation for life and helped them see things

in a better light. Only two subjects, a young girl who had been injured in an auto accident while on vacation and a male who had been drunk driving on a moped, viewed the experience as, "totally negative" and the "worse experience of my life". These subjects demonstrated some of the lowest perceived control scores and the highest stress scores. These incidental findings would appear to support Wallston's assertion that subjects perceive greater control over events which are viewed to have a positive outcome.

Predictability - The occurrence or non-occurrence of an event also impacts perceived control, with increased perceived control reported when events happen as expected rather than when they do not (e.g. birth of a child vs. infertility) (Jenkins & Ward, 1965). Greater perceived control also occurs when there is a close match between the environment and how the individual believes the world should be (Chein, 1972). While some studies fail to support the hypothesis (Padilla, 1981; Wallston et al, 1986); it has also been theorized that increased predictability is experienced when a subject is provided with prior information about a situation, leading to enhanced perceived control (Mills & Krantz, 1979).

The trauma patient is placed in a highly unpredictable situation with little opportunity to obtain preparatory information or prior experience. Given the highly unpredictable nature of the trauma environment it is interesting that the study subjects demonstrated such a high level of perceived control. This could have been a result of prior experience with critical illness and injury. Six subjects in the study admitted prior hospitalizations, and three had previous injuries requiring a hospital stay which may have increased the predictability of their current situation.

Preference for Control - While some theorists contend that the preference for control is determined by the intrinsic value of control and the driving motivation to attain it (i.e. control for its own sake) (deCharms, 1968; White, 1959), others propose that the preference for control is determined by its potential to be effective (Rodin et al, 1980). Rodin et al (1980) proposes that subjects will not work to achieve control in situations where they are already assured a desired outcome.

While the research on the preference for no control is limited, studies indicate that lack of control may be

preferred by subjects under certain conditions. When using control may require extra effort, time and/or attention; when information is lacking; when control is contrary to one's preferred style; when there is low probability of successful control; and/or when failure or disconfirmation of control occurs then control is less likely to be preferred and may even be stress producing (Thompson et al, 1991).

A preference not to control may also occur in situations where the subject perceives another person (e.g. nurse or doctor) to possess greater skill or experience in achieving a desired outcome. Burger et al (1986) illustrates this point in their study of blood drawing preference. When given the opportunity to draw their own blood or have the procedure done by an experienced phlebotomist, 70% of subjects preferred not to draw their own blood. When they were led to believe the phlebotomist was inexperienced only 38% chose to have their blood drawn by the phlebotomist, the remaining subjects choosing to do it themselves. These results indicate that the majority of subjects choose not to have control if a more effective

agent is available to whom control can be transferred, thereby ensuring greater potential for a successful outcome.

A preference for no control is similar to the concept of "secondary control" theorized by Rothbaum et al (1982) which contends that subjects achieve a sense of control by "giving up control" to powerful others (e.g. physicians and nurses) or a supreme being (e.g. God). The study subjects frequently expressed their confidence in the staff's ability to provide the care they required and indicated a willingness to "leave it up to the doctors and nurses". One elderly female subject expressed strong belief in God's intervention and willingness to put her "troubles in His hands." Another elderly subject expressed a belief in Fate and "what's going to happen, happens. No sense worrying about it, you can't change it."

This giving up of control to others may have been a major factor in the high level of perceived control seen in the study sample. Two of the younger subjects expressed frustration with their inability to control their situation and their mistrust in the staff to effectively meet their needs. These same subjects demonstrated decreased perceived control and high subjective stress.

Age and the importance of prior life experience may play a part in this giving up of control seen in the older subjects. Further exploration of this aspect of control is indicated, especially in the face of life-altering events like traumatic injury.

Perceived Control and Stress

Study results indicate that perceived control and subjective stress were negatively correlated suggesting that as perceived control increased, subjective stress decreased. These findings agree with previous human studies that have demonstrated the positive effect of increased perceived control in reducing subjective stress response.

The mediating influences of perceived control over the effects of stress have been widely studied. While some studies have failed to consistently support the hypothesis that perceived control reduces experimental stress (Padilla et al, 1981; Smith et al, 1986; Wallston, 1986) the majority of studies support the proposal that increased control reduces stress responses and increases well-being (Glass et al, 1971; Langer and Rodin, 1976; and Mills and

Krantz, 1979; Locke et al, 1984; Weisse, 1990; Wiedenfeld et al, 1990; Sieber et al, 1992).

Thompson et al (1991) has identified a variety of variables that influence the adaptiveness of perceived control and its ability to mediate the effects of a stressful situation. Two of these variables are: effort and attention; and self-responsibility Each variable can alter the individual's perception of control and thus attenuate its ability to mediate the effects of stress.

Effort and attention - Studies suggest that control options which require greater effort to initiate, also increase the subject's level of arousal. Solomon, Holmes and McCaul (1980) found that while subjects reported less anxiety upon receiving a painful shock if they perceived control via successful performance of a task, the desired effect was only seen if the control task required low effort by the subjects. A task which required a high level of effort by the subjects produced as much anxiety as the condition without a control task option.

Similar results were seen in studies which allowed avoidance of the administration of an unpleasant noise by performance of a difficult cognitive control task. Greater

physiological arousal was demonstrated in subjects performing the control task than subjects without a control option (Manuck et al, 1978). Stress, as measured by anxiety and physiologic arousal, appears to be increased when control options (intended to increase the perception of control) require a significant degree of effort and/or attention.

The amount of effort and attention required to achieve a sense of control is especially significant in the case of the trauma patient. Already physically and emotionally exhausted by their injuries, trauma patients may be too overwhelmed to actively deal with anything other than survival. For this reason they may rely heavily on secondary control, giving up control to powerful others like the nurses and doctors. In this manner they could achieve a sense of control, without wasting precious energy needed to heal.

Exhaustion and the need to "not deal with things right now" was expressed by three of the subjects in this study. As mentioned earlier, subjects frequently expressed trust in their caretakers and indicated a willingness to surrender control to their capable hands.

One subject became extremely agitated when his intravenous site was placed in the anticubital area of his dominant arm. With his other arm in a cast the subject felt every task became "impossible to do". He was unwilling to eat, bathe or even use the restroom until the intravenous site was changed, but he was also unwilling to request action. He expected the doctor and/or nurse "to know this is intolerable and come fix it". The subject also refused the second study blood draw at this point because he felt he "just couldn't deal with it right now".

Self-responsibility - Holding oneself responsible for negative outcomes in control situations may result in varied psychological consequences. Studies have demonstrated a wide range of responses to self-responsibility; with some subjects demonstrating maladaptive coping after assuming responsibility for negative outcomes (Meyer and Taylor, 1986), while others showed no relationship between self-responsibility and coping (Taylor et al, 1984) and a number demonstrated better coping following assumption of responsibility (Baum et al, 1983; Tennen et al, 1986).

Thompson and Janigian (1986) propose that in situations of self-responsibility or self-blame control attributions which arouse concern about one's abilities or dispositions (e.g. driver of a car that caused accident which killed other occupants) are strongly associated with poor psychological coping. Conversely, in situations which demand understanding why the event occurred and ascribing meaning to it (e.g. traumatic accidents), acknowledging self-responsibility can be a positive coping method since it allows the individual to perceive a measure of control over a seemingly uncontrollable event.

Four subjects in the study indicated they felt their injuries had occurred "for a reason". "I was not living my life right and God was trying to tell me something" reported one male subject who had been injured while driving a motorcycle while under the influence of alcohol. While demonstrating high perceived control scores, he also showed high subjective stress scores.

Another subject indicated she could not understand "how this could happen to me. I thought I was doing everything right in my life." She was on vacation and involved in an auto accident which resulted in a lacerated

liver. She described this incident as the "worst thing that has ever happened to me". This subject had low perceived control scores, high SACL, SACLVAS scores and elevated serum cortisol levels at both Time 1 and Time 2. These results support the study's original hypothesis which contends that subjects with low perceived control will experience more subjective and physiological stress response.

Several subjects (4) felt they had brought about their troubles by "doing something stupid." One male subject who had been stabbed in the abdomen outside a local bar indicated that he felt he had caused his own injuries by "getting drunk and stupid in a bad part of town, with the wrong people." He expressed a strong sense of responsibility not only for his injuries but also for his ultimate recovery. This subject also demonstrated high perceived control, low subjective stress and serum cortisol levels within the normal range.

Immunologic Data

While much of the trauma subjects' immune data failed to show a statistically significant difference when compared to normal subjects' values, a significant

difference was seen in the responsiveness of the mean fluorescence ratios for CD 14 cell surface receptors on monocytes after stimulation by all four stimulants (PMA, MDP, Con A, FMLP) at 15 and 60 minutes incubation. CD 25 on lymphocytes stimulated by PMA, MDP, Con A and FMLP at 15 minutes incubation also demonstrated a significant difference in receptor responsiveness when compared to normal subjects' data. These data were used as the outcome measure for immunity for this study.

CD 14 on Monocytes - The initial (baseline) increased responsiveness of mean fluorescence of CD 14 on monocytes noted in this study were similar to results reported by Spagnoli et al (1993) in a study of 6 multiple trauma patients with ISS scores over 20. Contrary to other post-injury studies (Kruger et al, 1991; Volk et al, 1993; Rabin et at, 1993), which show immediate decreases in CD 14 receptor responsiveness on monocytes after injury, Spagnoli et al (1993) reports a significant initial increase in CD 14 responsiveness on monocytes. The increased responsiveness noted by Spagnoli et al is almost identical to the results seen in this study, with a two-fold increase of CD 14 expression initially occurring on the monocytes of

trauma subjects' as compared to normal volunteers. This initial (baseline) increase was then followed by a decrease in responsiveness at the 15 and 60 minute incubations. Unlike the other studies, the Spagnoli study and this study measured CD 14 fluorescence levels after brief (less than 2 hours) mitogen incubations and analyzed monocyte response in lysed whole blood. These variations in technique and timing of analysis may have accounted for the differences seen.

In a series of preliminary studies it was determined that a brief 1 hour incubation was the optimal amount of time required to effect CD 14 responsiveness changes using the designated cell stimulants and Optilyse™ cell preparation technique. This brief incubation could have provided optimal stimulation of the cell surface markers, while preventing excessive shedding of CD 14 into the serum, as previously seen in other studies (Kruger et al, 1991; Volk et al, 1993; Rabin et at, 1993).

The use of lysed whole blood for analysis may have also played a role in these results. Monocytes were left in their normal milieu rather than separated out for study,

allowing lymphocytes and their interleukins to influence the behavior of the monocytes and their cell surface receptors (Volk et al, 1993).

CD 25 on Lymphocytes - Like the study conducted by Teodorczyk-Injeyan et al (1987), in this study we demonstrated a decreased responsiveness of CD 25 receptors on lymphocytes stimulated by Con A after 15 minutes of 37 degree incubation. While CD 25 responsiveness in the Teodorczyk-Injeyan study was decreased after 72 hours of incubation in Con A, the results of this study demonstrated decreased responsiveness of CD 25 expression after only 1 hour of Con A incubation. While these changes are small and could be the result of "noise" in the flow cytometry analysis, they are consistently seen, statistically significant and mirror the results demonstrated by Teodorczyk-Injeyan et al (1987). These results suggest a decreased responsiveness of CD 25 occurred following traumatic injury in the sample population.

Perceived Control, Subjective Stress and Immunity

In this study there were statistically significant correlations between perceived control, subjective stress response and immunity. An increase in subjective stress

was negatively correlated with decreased responsiveness of mean fluorescence ratios of CD 14 on monocyte and CD 25 on lymphocytes. Conversely, increased perceived control positively correlated with increased responsiveness of mean fluorescence ratios of CD 14 on monocytes. While the use of CD cell surface receptor responsiveness is a relatively new measure of immune function, the findings in this study are similar to trends previously established in the stress, control and immunity literature. Subjects presented with an uncontrollable stressor demonstrated increased subjective stress and negative mood states (Locke et al, 1984; Weisse et al 1990) increased serum cortisol and catecholamines (Wiedenfel et al, 1990); and elevated plasma ACTH and urine cortisol (Cruse et al 1992). These findings correlated with decreases in natural killer cell activity (Locke et al, 1982; Cruse et al, 1992; Sieber et al, 1992); diminished lymphocyte proliferation and T cell numbers ((Weisse et al, 1990; Wiedenfel et al, 1990; Cruse et al, 1992); decreased interleukin 2 levels (Cruse et al, 1992) and reduced monocyte percentages (Weisse et al, 1990). The relationships seen between perceived control, subjective stress response and immune responsiveness in this study

provide new evidence to support the hypothesis that perceived control may mediate the relationship between stress and immunity.

Alternative Explanations and Issues Concerning Validity

Study Limitations

Sample size - The small sample size of this study posed a major limitation in interpretation of the findings. Original calculations indicated a sample N of 90 subjects was necessary to detect significant findings with a power of .80. The projected sample size was not feasible to enroll and therefore, it was decided to explore the nature of the relationships between independent and dependent variables using correlation statistics.

Sample size became an especially critical issue when considering the physiologic stress and immune correlates. Because two subjects dropped out of the study at Time 2, only eight subjects' results were used in statistical analysis of these variables. The small sample size made it difficult to detect statistically significant relationships between serum cortisol, measures of immune response and other variables in the study.

Timing of data collection - There were no statistically significant changes in any of the study variables between Time 1 (early post injury) and Time 2 (late post injury) data collection points. The lack of change may have been due to the small sample size, but may also have been due to inappropriate timing of the data collection. The original intent was to collect early injury phase data within the first 24 hours after injury and late injury phase data at 96 hours post-injury. The goal was to obtain immediate post-injury baseline values and compare this to values obtained 4 days after injury when immune dysfunction is likely to occur. Unfortunately the immediate post-injury period became complicated with anesthesia effects, intubation and other conditions that prohibited oral communication with the patient. The actual early injury data collection occurred 48 hours after injury. As a result, the high stress response anticipated in the early hours after injury may have been missed and/or not enough time may have elapsed between data collection points to allow for significant change in the variables.

Subjective stress - While subjective stress response as measured by the Stress/Arousal CheckList was elevated

above the normative mean indicating increased subjective stress, the Stress/Arousal CheckList Visual Analogue Scale indicated that subjects' stress fell well within the normal range. These contradictory results may have been due to testing error secondary to the repeated measure design of the study, but this appears unlikely since scores for each measure demonstrated little change between Time 1 and Time 2. Reactivity (Woods et al, 1988) may also have been a problem causing subjects to give the answers they thought were desired by the researcher, especially on the Visual Analogue Scale where subjects may have been tempted to give more positive responses.

Serum cortisol - While serum cortisol, the physiologic correlate of stress, was elevated it failed to demonstrate any significant relationships with the other study variables. This lack of statistical significance is contrary to findings in the general stress and immunity literature and fails to support a key hypothesis of this study which proposed an increase in serum cortisol would positively correlate with an increase in subjective stress.

These findings may be a result of the small sample size (eight subjects) and the large standard deviations

seen at Time 1 (SD 8.9) and at Time 2 (SD 5.3). This could have been corrected by increasing the sample size, thus diluting the effect of extreme individual scores.

Serum cortisol did positively correlated with a physiologic measure of illness severity, the APACHE score, indicating that as illness severity increased so did serum cortisol. These findings suggest that greater illness severity in the sample would have caused increased physiologic stress resulting in higher serum cortisol values.

Measures of immunity - A potential limitation to this study is the validity of the immune measures used. While the use of cell surface receptor responsiveness to selected stimulants is well documented in the literature as a valid measure of immune function (Tellado-Rodriguez et al, 1988; Ogle et al 1989; Bach, 1990; Peck et al, 1990; Dunn, 1993), the protocol used in this study had never been used before. Although the protocol used a combination of techniques widely documented in the literature, and normative values were established for this study by including nine normal, non-injured subjects, further testing of the immune cell stimulation protocol with larger and different subject

samples is necessary. Once normative responses are documented and confirmed in both injured and noninjured samples, these techniques can be applied with greater confidence.

Immune function - Only three measures of immunity out of a possible eight were statistically correlated with subjective stress (SACL, SACLVAS) and perceived control. This may have been a result of error in the timing of the sample collection. Changes in granulocytes' cell surface receptor responsiveness may have occurred too quickly in the trauma course to demonstrate changes at the 48 and 96 hour data collection points. Similarly, early changes in lymphocyte populations secondary to the influences of epinephrine may have been missed, while more long-term changes as the result of cortisol's impact may not yet have occurred.

Finally, the absence of cellular changes may be a response to the stress of traumatic injury that may have blunted the cells ability to respond to the challenge presented by the cell stimulants. This blunting effect or "turning off" of immune cell responses may be a protective function designed to prevent a hyper-response of the immune

system to an overwhelming challenge (Horn, 1995). This concept requires further investigation.

Potential Stressors of Hospitalization - A number of variables appeared to impact the study results. Days in the ICU correlated with both of the subjective stress variables and two of the immune status measures, suggesting that the number of days spent in the ICU was a stressor that increased the amount of subjective stress experienced and decreased cellular immune response.

The number of narcotics subjects received negatively correlated with two measures of immune status suggesting that narcotic use had an immunosuppressive impact on immune status as measured by CD 14 receptor fluorescence on monocytes.

The number of narcotics subjects received also strongly correlated with the number of antibiotics given suggesting that increased narcotic use is related to signs and symptoms of infection/sepsis, for which the increased number of antibiotics were given. Both of the relationships between narcotics use and CD 14 on monocytes mean fluorescence response and the relationship between narcotic

use and number of antibiotics given suggest a possible link between narcotic use and immunity and sepsis.

The number of antibiotics given also correlated significantly with the number of blood transfusions received. This strong positive correlation suggests that the increased number of antibiotics were given in response to clinical signs and symptoms of infection/sepsis that may be in some way caused by the number of blood transfusions given. This may also be an incidental finding secondary to the increased severity of the subjects' illness which requires greater numbers of antibiotics and blood.

A statistically significant positive correlation between the number of NSAIDS given and down-regulation of CD 25 on lymphocytes responsiveness indicates a link between increased NSAID use and decreased lymphocyte response, a phenomena previously documented in the literature (Cook et al, 1993).

The correlations between number of procedures done and the mean fluorescence response of CD 14 on monocytes and CD 25 on lymphocytes suggest a link between the number of stressful procedures a subject experiences and cellular immune response. It appears that the more procedures done

following traumatic injury the less responsive the subject's immune status (as measured by mean fluorescence of CD 14 and 25 on monocytes and lymphocytes).

Conclusions and Implications

This study was designed to examine the relationships among perceived control, stress response, and immune response after traumatic injury. It was proposed that a high level of perceived control would positively correlate with a decrease in stress response and a change in immune status between two time points. These results were partially substantiated by the study findings. Perceived control and subjective stress were negatively correlated. Subjective stress decreased as perceived control increased. While the physiologic stress correlate, serum cortisol, was elevated at both data collection points, it failed to correlate significantly with any of the other study variables. Three of the eight immune measures correlated significantly with both subjective stress and perceived control. Given these results it appears that increased perceived control does modify subjective stress response and ultimately immune function. However, any interpretations or implication of these results must be

made within the context of the study's unique characteristics, limitations and validity issues.

Generalizability of these results to the larger trauma population is a possibility. While the study sample reflected only moderate injuries with a mean ISS of 15.9 (SD 8.4) and a mean APACHE score of 5.8 (SD 3.19), a fairly broad cross-section of diagnoses and mechanisms of injuries were represented, indicating these results could be applied to a relatively large trauma population.

Recommendations for Further Study

The results of this study presented more questions than answers. Future studies should focus on four areas: defining the psychological implications of traumatic injury and mechanisms used by subjects to cope; refining perceived control measurement; refining the immune function protocol and applying it to a large number of normal and traumatized subjects; and implementing an experimental study design which introduces various types of control interventions to both trauma and elective surgery subjects.

A qualitative approach is indicated to study the multiple psychological implications of traumatic injury and subjects coping mechanisms. My brief discussion with each

subject revealed an untapped source of information about how patients cope with life altering events, which could provide valuable insight for both trauma patients and other populations enduring similar stress.

Further refinement of the perceived control measure is indicated, especially to address the unique stressors faced in the hospital setting. A tool which identifies individual preferences for control would be beneficial in an experimental study to identify the impact of nursing interventions to increase perceived control.

The immune function protocol requires further refinement of its techniques and application to a larger population. Certain cell stimulants that proved ineffective could be eliminated and CD antigens that demonstrate quicker response to these cell stimulants could be substituted.

Finally, a variety of control interventions (e.g. open visiting hours in the ICU; patient-controlled analgesia pumps; control over sleep pattern) should be tested using an experimental study design which compares stress and immunity responses of trauma and elective surgery subjects.

Results of this study have demonstrated the existence of significant relationships among perceived control, stress and immunity. It has increased the scientific knowledge of how these variables relate to one another and poses compelling questions for future study. Continued scientific investigation is required to identify the potential benefits of interventions which can modify these relationships.

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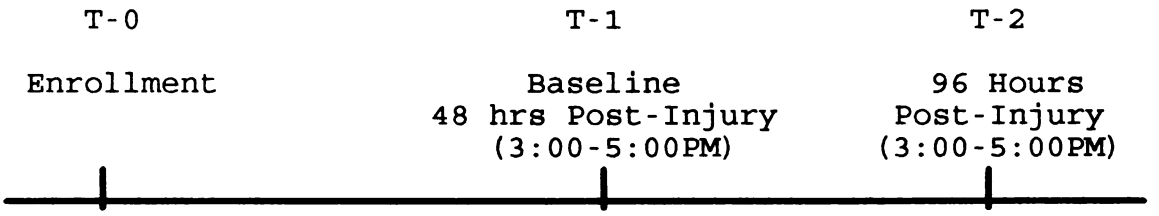
APPENDIX A

STUDY TIMELINE

STUDY TIMELINE



T-0	T-1	T-2
Within 48 hrs. of initial injury: determine ISS & CFS, enroll* in study, obtain consent, place skin tests(read at 48 and 72 hrs.post placement).	Assess CFS, administer SACL & WECSS, draw blood for serum cortisol/immune measures.	Assess CFS, administer SACL & WECSS, draw blood for serum cortisol/immune measures, determine APACHE II score,finish demographic data

CFS = Cognitive Function Scale
ISS = Injury Severity Score
WECSS = Wallhagen's Experience of Current Situation Subscale
SACL = Stress/Arousal Check List

*Principal investigator will be on call until 8pm, subjects arriving after 8pm will be enrolled after 10am the next morning.

APPENDIX B

STRESS/AROUSAL ADJECTIVE CHECKLIST
WALLHAGEN'S EXPERIENCE OF CURRENT SITUATION SUBSCALE
THE ABBREVIATED INJURY SCALE
APACHE II ILLNESS SEVERITY SCALE
RANCHO LOS AMIGOS COGNITIVE FUNCTION SCALE

#_____
1

STRESS/AROUSAL ADJECTIVE CHECKLIST

Please answer each of the following questions according to ***how you feel right now.*** Answer each item by marking the response to indicate if the answer is:

Definitely Yes..... ++
Slightly Yes..... +
Not Sure/Don't Understand..... ?
Definitely Not..... -

1.	calm	++	+	?	-	11.	uptight	++	+	?	-
2.	contented	++	+	?	-	12.	drowsy	++	+	?	-
3.	active	++	+	?	-	13.	tense	++	+	?	-
4.	vigorous	++	+	?	-	14.	relaxed	++	+	?	-
5.	comfortable	++	+	?	-	15.	passive	++	+	?	-
6.	lively	++	+	?	-	16.	energetic	++	+	?	-
7.	uneasy	++	+	?	-	17.	alert	++	+	?	-
8.	tired	++	+	?	-	18.	bothered	++	+	?	-
9.	aroused	++	+	?	-	19.	sleepy	++	+	?	-
10.	worried	++	+	?	-	20.	distressed	++	+	?	-

Now please place a / to indicate your position along the two lines below. Respond as you ***feel right now.***

Comfortable
or calm ——————————————————— Worried

Active ——————————————————— Sleepy

Stress/Arousal Check List. Adapted from: King, M. Stanley, G., Burrows, W. (1987) **Stress- Theory and Practice.** Sydney, Australia: Grune and Stratton, Inc.

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2

Wallhagen's Experience of Current Situation Subscale

I am interested in how you are experiencing your current situation. I am going to read you a list of statements that may or may not describe how you feel. As I read each statement I would like you to tell me if you agree or disagree with it. After you decide if you agree or disagree, I will ask you if you moderately or strongly agree or disagree.

Let's begin with (Read first item). **Do you agree or disagree? Moderately or strongly?**

	AGREE		**DISAGREE**	
	Strongly	**Moderately**	**Moderately**	**Strongly**
1. I am able to handle my current situation.	1	2	3	4
2. I accomplish what I have to do.	1	2	3	4
3. In my situation I can choose how I want to manage things.	1	2	3	4
4. My current situation is under control.	1	2	3	4
5. I have adequate coping skills to meet current demands.	1	2	3	4
6. I accomplish things in my daily life that are important to me.	1	2	3	4
7. I can change how I respond to the demands of my current situation when I feel I need to.	1	2	3	4

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3

	AGREE		DISAGREE	
	Strongly	Moderately	Moderately	Strongly
8. Everything is running smoothly.	1	2	3	4
9. I am on top of things.	1	2	3	4
10. I can change things when I need to.	1	2	3	4
11. I feel good about how I am dealing with things.	1	2	3	4
12. Things are going along as planned.	1	2	3	4
13. I have the resources I need to deal with my situation.	1	2	3	4

The Abbreviated Injury Scale

AIS SCORE	1 MINOR	2 MODERATE	3 SEVERE NOT LIFE THREATENING	4 SEVERE: LIFE THREATENING	5 CRITICAL SURVIVAL UNCERTAIN
HEAD/NECK	PI = PENETRATING INJURY	PI to neck with no organ involvement	Complex PI to neck with tissue loss/organ involvement Minor lac. carotid/vertebral A; internal jugular V Transection & segmental loss jugular V Thyroid laceration Superficial lac. larynx/pharynx Cord contusion with transient neurological signs	Minor lac. carotid/vertebral A with neurological deficit Transection carotid/vertebral A; int jugular V Segmental loss int. jugular vein Perforation larynx/pharynx Cord contusion with incomplete cord syndrome	PI with entrance and exit wounds PI of cerebrum/cerebellum Segmental loss carotid/ vertebral A Complex laceration larynx/ pharynx Cord laceration Complete cord lesion
FACE	PI with no tissue loss	PI with superficial tissue loss Corneal/scleral lac.	PI with major tissue loss		
THORAX	PI with no violation of pleural cavity	Thoracic duct laceration Pleural laceration	Complex PI but no violation of the pleural cavity Sub. lac. innominate/pulmonary/ subclavian and other named smaller veins Sub. lac. trachea/bronchus/ esophagus Lung laceration 01 lobe Unilateral h' or p'thorax Diaphragmatic laceration Cord contusion with transient neurological signs	Sup. aortic laceration Major lac. innominate/ pulmonary/subclavian and other named smaller art; vena cava/brachiocephalic pulmonary/subclavian and other names smaller veins Transection/tissue loss other named smaller veins Perforation trachea/bronchus esophagus Multilobar lung laceration H'p'mediastinum Bilateral h'p'thorax Tension p'thorax H'thorax >1000 cc Cardiac tamponade Cord contusion with incomplete cord syndrome	Major aortic laceration Transection/segmental loss vena cava/pulmonary/ brachiocephalic V. & other named smaller arteries Lac. trachea/bronchus/ esophagus with tissue loss Multilobar lung lac. with tension p'thorax/ >1000cc Myocardium/valve laceration Cord laceration Complete cord lesion
ABDOMEN	PI with no peritoneal penetration	PI with superficial tissue loss but no peritoneal penetration Sub. lac. stomach/SB/ mesentery/bladder/ ureter/kidney/liver/ spleen/pancreas Laceration through peritoneum	PI with significant tissue loss but no peritoneal penetration Sub. lac. vena cava/iliac and other named smaller arteries and veins Sub. lac. duodenum/colon/rectum Full thickness laceration SB/ mesentery/bladder/ureter Major lac. or minor lac. with major vessel injury/>1000cc h'peritoneum; kidney/liver/ spleen/pancreas Cord contusion with transient neurological signs	Minor aortic laceration Major lac. vena cava/iliac A & V and other named smaller arteries and veins Transection/segmental loss iliac and other named smaller veins Full thickness lac. stomach/ colon/duodenum/rectum Tissue loss/gross contamination stomach/SB/mesentery bladder/ureter Cord contusion with incomplete cord syndrome	Major aortic laceration Transection/segmental loss vena cava/iliac and other named smaller arteries Tissue loss/gross contamination duodenum/ colon/rectum Tissue loss kidney/liver spleen pancreas Cord laceration
EXTREMITIES	Sup. lac. brachial and other named veins	Simple PI with no internal structure involvement Sub. lac. axillary/ brachial/popliteal A; axillary/femoral/ popliteal V. Major lac. & segmental loss brachial vein and other named smaller arteries and veins Lac. median/radial/ ulnar/femoral/tibial/ peroneal N Major tendon/muscle lac.	Complex PI with internal structure involvement Sub. laceration femoral A. Major lac. axillary/popliteal A; axillary/femoral/popliteal V. Segmental loss axillary/ femoral popliteal V. Sciatic nerve laceration PI nerve lac. in same extremity Multiple tendon/muscle lacerations in same extremity	Major lac. brachial/femoral artery Segmental loss brachial/ axillary/popliteal artery	Segmental loss femoral A.
EXTERNAL	Superficial laceration ≤5 cm on face or hand ≤10 cm on body PI with no tissue loss	Laceration >5 cm on face hand or >10 cm on body PI with superficial tissue loss			

AIS = 6 MAXIMUM INJURY
AUTOMATICALLY ASSIGNED ISS = 75

HEAD/NECK Brainstem laceration

THORAX Aortic transection
Segmental loss aorta/innominate pulmonary/subclavian arteries
Complex myocardial laceration

ABDOMEN Aortic transection/segmental loss

AIS 85

INJURY SEVERITY SCORE (I.S.S.)

I.S.S. BODY REGION	A.I.S. SCORE	SQUARED
HEAD/NECK		
FACE		
THORAX		
ABD/PELVIC CONTENTS		
EXTREMITIES/PELVIC GIRDLE		
EXTERNAL		
I.S.S. (sum of squares of 3 most severe only)		

AIS SCORE	1 MINOR	2 MODERATE	3 SEVERE NOT LIFE THREATENING	4 SEVERE LIFE THREATENING	5 CRITICAL SURVIVAL UNCERTAIN
HEAD/NECK	Headache/dizziness 2° to head trauma Cervical spine strain with no fracture or dislocation	Amnesia from accident Lethargic/stuporous/ obtunded; can be roused by verbal stimuli Unconsciousness <1 hr Simple vault fracture Thyroid contusion Brachial plexus injury Dislocation or fracture spinous or transverse process of C-spine Minor compression fracture (≤20%) C-spine	Unconsciousness 1-6 hrs Unconsciousness <1 hr with neurological deficit Fracture base of skull Comminuted compound or depressed vault fracture Cerebral contusion/subarachnoid hemorrhage Intimal tear/thrombosis carotid A. Contusion larynx, pharynx Cervical cord contusion Dislocation or fracture of lamina body, pedicle or facet of C-spine Compression fracture >1 vertebra or >20% anterior height	Unconsciousness 1-6 hrs with neuro deficit Unconsciousness 6-24 hrs Appropriate response only to painful stimuli Fractured skull with depression >2 cm, tore dura or tissue loss Intracranial hematoma ≤100 cc Incomplete cervical cord lesion Larynageal crush Intimal tear/thrombosis carotid A with neuro. deficit	Unconsciousness with inappropriate movement Unconscious >24 hrs Brain stem injury Intracranial hematoma >100cc Complete cervical cord lesion C4 or below
FACE	Corneal abrasion Sup. tongue laceration Nasal or mandibular ramus* fracture Tooth fracture/avul. sion or dislocation	Zygoma, orbit*, body* or subcondylar mandible* fracture LeFort I fracture Scleral/corneal laceration	Optic nerve laceration LeFort II fracture	LeFort III fracture	
THORAX	Rib fracture* Thoracic spine strain Rib cage contusion Sternal contusion *Add AIS 1 if associated with h'thorax, p'thorax or h'p'mediastinum	2-3 rib fractures* Sternum fracture Dislocation or fracture spinous or transverse process T-spine Minor compression fracture (≤20%) T-spine	Lung contusion/lac. 01 lobe Unilateral h' or p'thorax Diaphragm rupture ≥4 rib fractures* Intimal tear/minor lac/thrombosis subclavian or innominate A. Inhalation burn, minor Dislocation or fracture of lamina body, pedicle or facet of T-spine Compression fracture >1 vertebra or more than 20% height Cord contusion with transient neurological signs	Multilobar lung contusion or laceration H'p'mediastinum Bilat. h'p' thorax Flail chest Myocardial contusion Tension p'thorax Hemothorax >1000 cc Tracheal fracture Intimal aortic tear Major lac. subclavian or innominate A. Incomplete cord syndrome	Major aortic laceration Cardiac laceration Ruptured bronchus/trachea Flail chest/bilat. bure requiring mechanical support Laryngotrach. separation Multilobar lung laceration with tension p'thorax h'p'mediastinum, or >1000cc hemothorax Cord laceration or complete cord lesion
ABDOMEN	Abrasion/contusion superficial lac. scrotum, vagina, vulva, perineum Lumbar spine strain Hematuria	Contusion/sup. laceration stomach, mesentery, SB bladder, ureter, urethra Minor contusion/lac. kidney, liver, spleen pancreas Contusion duodenum/colon Dislocation or fracture spinous or transverse process L-spine Minor compression fracture (≤20%) L-spine Nerve root injury	Sup. lac duodenum/colon/rectum Perforation SB/mesentery/bladder ureter/urethra Major contusion/or minor lac. with major vessel involv., or h'peritan. >1000 cc of kidney/liver/spleen/panc Minor iliac A. or V. laceration Retroperitoneal hematoma Dislocation or fracture of lamina body, facet, or pedicle of L-spine Compression fracture >1 vertebra or >20% anterior height Cord contus. with trans neuro signs	Perforation stomach duodenum/colon/rectum Perforation with tissue loss stomach/bladder SB/ureter/urethra Major liver laceration Major iliac A. or V. lac. incomplete cord syndrome Placental abruption	Major lac. with tissue loss or gross contamination of duodenum/colon/rectum Complex ruoture liver, spleen/kidney/pancreas Complete cord lesion
EXTREMITIES	Contusion elbow, shoulder, wrist, ankle Fracture/dislocation finger, toe Sprain A-C joint, shoulder, elbow, finger, wrist, hip ankle, toe.	Fracture humerus*, radius* ulna*, fibula, tibia*, clavicle, scapula, carpals metacarpals, calcaneus tarsals, metatarsals, pubic rami or simple pelvic fracture Dislocation elbow, hand, shoulder, A-C joint Major muscle/tendon.lac. Intimal tear/minor lac. axillary, brachial, popliteal A; axillary, femoral, popliteal V	Comminuted pelvic fracture Fractured femur Dislocation wrist/ankle/knee/hip Below knee or upper extremity amputation Rupture knee ligaments Sciatic nerve laceration Intimal tear/minor lac. femoral A. Major lac. ± thrombosis axillary or popliteal A; axillary, popliteal or femoral V.	Pelvic crush fracture Traumatic above knee amputation/crush injury Major laceration femoral or brachial artery	Open pelvic crush fracture *Add AIS 1 to these fractures if open, displaced or comminuted
EXTERNAL	Abrasions/contusions ≤25 cm on face/hand ≤50 cm on body Superficial lacs. ≤5 cm on face/hand ≤10 cm on body 1° burn up to 100% 2° or 3° burn/deglov. injury<10% tot. body	Aprasions/contusions >25 cm on face or hand >50 cm on body Laceration >5 cm on face or hand >10 cm on body 2° or 3° burn or degloving injury 10-19% of total body	2° or 3° burn or degloving injury 20-29% of total body	2° or 3° burn or degloving injury 30-39% total body	2° or 3° burn or degloving injury 40-89% total body

AIS=6 MAXIMUM INJURY
AUTOMATICALLY ASSIGNED I.S.S.=75

HEAD/NECK Crush fracture, crush/laceration brain stem
Decapitation
Cord crush/laceration or total transection with or without fracture C3 or above

THORAX Total severance aorta
Chest massively crushed

ABDOMEN Torso transection

EXTERNAL 2° or 3° burn or degloving injury 90% T.B.S.

INJURY SEVERITY SCORE (I.S.S.)

I.S.S. BODY REGION	A.I.S. SCORE	SQUARED
HEAD/NECK		
FACE		
THORAX		
ABD/PELVIC CONTENTS		
EXTREMITIES/PELVIC GIRDLE		
EXTERNAL		
I.S.S. (sum of squares of 3 most severe only)		

THE APACHE II SEVERITY OF DISEASE CLASSIFICATION SYSTEM

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE — rectal (°C)	≥ 41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤ 29.9°
MEAN ARTERIAL PRESSURE — mm Hg	≥ 160	130-159	110-129		70-109		50-69		≤ 49
HEART RATE (ventricular response)	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
RESPIRATORY RATE — (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
OXYGENATION A-aDO$_2$ or PaO$_2$ (mm Hg) a FIO$_2$ ≥ 0.5 record A-aDO$_2$	≥ 500	350-499	200-349		< 200				
b FIO$_2$ < 0.5 record only PaO$_2$					PO$_2$ > 70	PO$_2$ 61-70		PO$_2$ 55-60	PO$_2$ < 55
ARTERIAL pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
SERUM SODIUM (mMol/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110
SERUM POTASSIUM (mMol/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	≥ 3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
HEMATOCRIT (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
WHITE BLOOD COUNT (total/mm3) (in 1,000s)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
GLASGOW COMA SCORE (GCS) Score = 15 minus actual GCS									
A Total ACUTE PHYSIOLOGY SCORE (APS) Sum of the 12 individual variable points									
Serum HCO$_3$ (venous mMol/L) (Not preferred, use if no ABGs)	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	< 15

B AGE POINTS:
Assign points to age as follows

AGE(yrs)	Points
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6

C CHRONIC HEALTH POINTS
If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:
a for nonoperative or emergency postoperative patients — 5 points
or
b for elective postoperative patients — 2 points

DEFINITIONS
Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria:

LIVER Biopsy proven cirrhosis and documented portal hypertension, episodes of past upper GI bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties, or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.

RENAL Receiving chronic dialysis

IMMUNO-COMPROMISED The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS

APACHE II SCORE
Sum of A + B + C

A APS points _____

B Age points _____ _____

C Chronic Health points _____

Total APACHE II _____

Rancho Los Amigos Cognitive Function Scale

Levels of Cognitive Functioning

Level I. no response: Patient appears to be in a deep sleep and is completely unresponsive to any stimuli.

Level II. generalized response: Patient reacts inconsistently and nonpurposefully to stimuli in a nonspecific manner. Responses are limited and are often the same regardless of stimulus presented. Responses may be physiologic changes, gross body movements, and/or vocalization.

Level III. localized response: Patient reacts specifically but inconsistently to stimuli. Responses are directly related to the type of stimulus presented. Patient may follow simple commands such as "close eyes" or "squeeze hand" in an inconsistent, delayed manner.

Level IV. confused and agitated response: Patient acts bizarre and nonpurposeful in relation to his or her immediate environment. Patient does not discriminate among persons or objects and is unable to cooperate directly with treatment efforts. Vocalization is frequently incoherent or inappropriate to the environment, and the patient may confabulate. Gross attention to the environment is very short, and the patient often has no selective attention. Patient lacks short-term recall.

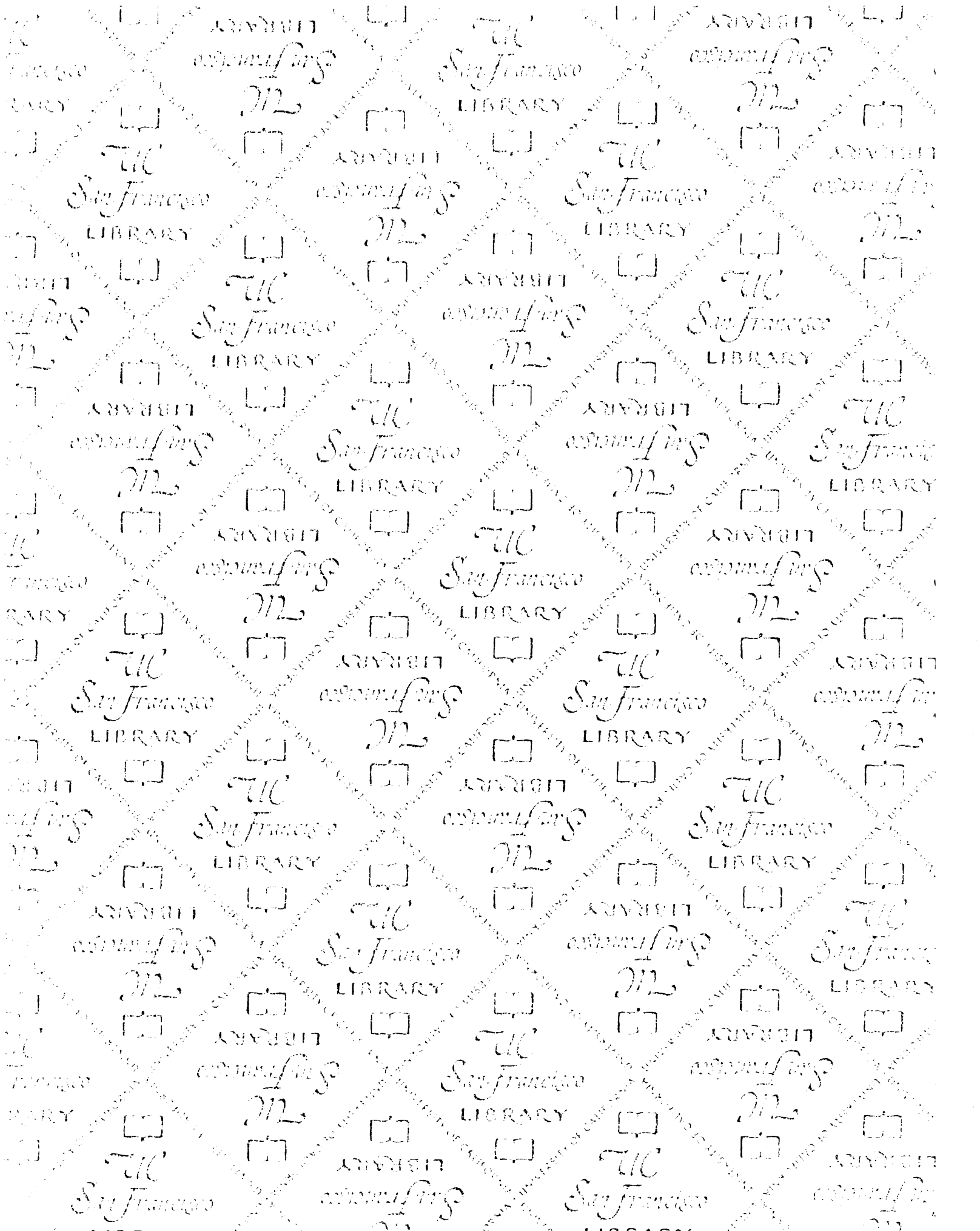
Level V. confused, inappropriate, and nonagitated response: Patient is able to respond to simple commands fairly consistently. However, with increased complexity of commands or lack of any external structure, responses are nonpurposeful, random, or fragmented. Patient pays gross attention to the environment but is highly distractible and lacks ability to focus attention on a specific task. With structure, patient may be able to converse on a social-automatic level for short periods of time, but vocalization is often inappropriate and confabulatory. Memory is severely impaired and patient often shows inappropriate use of objects. Patient may perform a previously learned task with structure but is unable to learn new information.

Level VI. confused and appropriate response: Patient shows goal-directed behavior but is dependent on external input for direction. Patient follows simple directions consistently and carries over information for relearned tasks but usually not for new tasks. Responses may be incorrect because of memory problems but appropriate to the situation. Past memories show more depth and detail than recent memory.

Level VII. automatic and appropriate response: Patient shows appropriate behavior and appears oriented within hospital and home settings and goes through daily routine automatically but is frequently robotlike, with minimal-to-absent confusion, and has shallow recall of activities. Patient carries over information for new learning but at a decreased rate. With structure, patient is able to initiate social or recreational activities. Judgment remains impaired.

Level VIII. purposeful and appropriate response: Patient is able to recall and integrate past and recent events and is aware of and responsive to environment. Patient carries over information for new learning and needs no supervision once activities are learned. Patient may continue to show decreased ability, relative to premorbid abilities, in abstract reasoning, tolerance to stress, and judgment in emergencies or unusual circumstances.

Note: Adapted with permission from Hagen C: Language disorders secondary to closed head injury: Diagnosis and treatment. *Top Lang Disord* 1981;1:73–87.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