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Immune function and psychological distress in familial dementia caregivers: A controlled trial of a cognitive -behavioral intervention

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IMMUNE FUNCTION AND PSYCHOLOGICAL DISTRESS IN FAMILIAL
DEMENTIA CAREGIVERS: A CONTROLLED TRIAL OF A
COGNITIVE-BEHAVIORAL INTERVENTION

by

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Master of Arts
Pepperdine University
1999

Master of Arts
University of Nevada Las Vegas
2003

A dissertation submitted in partial fulfillment
of the requirements for the

Doctor of Philosophy Degree in Psychology
Department of Psychology
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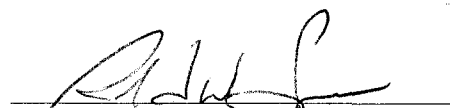
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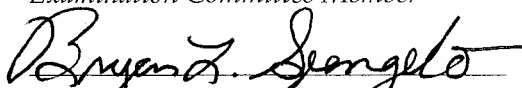
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ABSTRACT

Immune Function And Psychological Distress In Familial Dementia Caregivers: A Controlled Trial Of A Cognitive-Behavioral Intervention

by

Kevin M. Lancer, M.A.

Dr. Douglas Ferraro, Examination Committee Chair
Professor of Psychology
University of Nevada, Las Vegas

Recent data on the prevalence of Alzheimer's disease estimate that sufferers could number as high as 4.78 million; that number is expected to quadruple by the year 2050. The vast majority of persons with dementia reside in the community, able to do so because of the care received from their families. The increase in the number of the elderly dependent on others for assistance will continue to increase, straining already limited individual and societal resources. The subjects of this study were Alzheimer's disease and related dementia (ARD) familial caregivers, representing a portion of society needing assistance and that is growing both in sheer numbers and overall percentage of the population. Caregivers dealing with the symptoms of a gradual, progressive, irreversible neurodegenerative disease such as Alzheimer's face numerous emotional, psychological, social, and financial demands that classify ARD caregiving as a chronic stressor. In addition, familial caregivers are often elderly themselves, and are at an

increased risk for injury, illness, and they face an exacerbation of already declining immune system function due to chronic stress.

This study was an attempt to enhance immune system functioning and reduce subjective stress levels in the familial caregivers of Alzheimer's disease and related dementia (ADRD) patients. In order to accomplish that objective, a controlled comparison between a cognitively based stress management intervention (CBSM) and a no-treatment control group was conducted. This study also attempted to make a contribution to the existing body of knowledge in the field of psychoneuroimmunology (PNI) by addressing the complicated inter-relationship between psychological stress and immune system functioning. To that end, study participants were tested with several measures of psychological performance, such as the Center for Epidemiological Studies-Depression (CES-D), the Ways of Coping-Revised (WOCR), Profile of Mood States (POMS), and the Personal Views Survey III-Revised (PVS-III-R), as well as one measure of immune system function, plasma levels of interleukin-6.

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In life, sometimes decisions are made that are pivotal. Marriage has been one of those decisions for me. To say that I couldn’t have accomplished this Ph.D. without my wife isn’t true; to say that it would have been a vastly different, much less rich experience without her is a profound understatement. My Rebekah is like the sweetness in the breeze, the color in the fall, the movement in the ocean to me. Everything she touches, she adds to. Without her, I would be simply another man with a degree; with her, I am the owner of a treasure chest of memories, experiences, and love. And the visible presence of that love is our three sons, Dyroen, Thomas, and William. To my wife and sons, thank you.

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CHAPTER 1

INTRODUCTION

This study was an attempt to enhance immune system functioning and reduce subjective stress levels in the familial caregivers of Alzheimer's disease and related dementia (ADRD) patients. In order to accomplish that objective, a controlled comparison between a cognitively based intervention and a no-treatment control group was conducted. The unique contribution of this study to the literature was in examining the effects of a cognitive behavioral stress management (CBSM) intervention on caregiver subjective distress and caregiver immune system functioning. No other published studies have examined the effect of a psychosocial intervention on caregiver stress reduction and enhanced immune function using IL-6 as a dependant measure of immune system function.

This study also attempted to contribute to the existing body of knowledge in the field of psychoneuroimmunology (PNI) by addressing the complicated inter-relationship between psychological stress and immune system functioning. PNI developed from a multitude of studies linking immune system function with the interaction between psychological states, the central nervous system (CNS) and the endocrine system (Garand, 2000). This study was also designed to follow recommendations for future

research made by current leaders in the field of PNI as described below. Issues of interest in intervention studies include client characteristics (health, SES, age, stressors); intervention components (relaxation, cognitive-behavioral, social support, religion, peer support); and intervention characteristics (individual vs. group, frequency, duration). Janice Kiecolt-Glaser and her colleagues state “A growing literature supports the hypothesis that psychosocial factors have clinically significant relationships with immune-related health outcomes...” (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002, p.540). Additionally, they go on to recommend that “future work should identify and examine immune measures that are directly relevant to particular health conditions” (p. 541).

The participants in this study (ADRD familial caregivers) represent a portion of society potentially needing assistance and that is growing both in sheer numbers and overall percentage of the population. In 1999, the United States Administration on Aging (U.S. AOA, 1998a; U.S. AOA, 1998b) estimated that there were 34.7 million persons over the age of 65 in this country and that there will be 61.9 million by 2025. Although

Alzheimer’s disease is not a normal part of aging, it should be noted that it is clearly an age-related disorder (Grant, Adler, Patterson, Dimsdale, Ziegler, & Irwin, 2002). Of those 34.7 million persons over the age of 65 in the United States, epidemiological research shows that 10% of those over age 65, and nearly 50% of those over the age of 85 have either Alzheimer’s disease or a related form of dementia (U.S. AOA, 1998b, Dunkin & Hanley, 1998). Recent data on Alzheimer’s disease prevalence estimate that sufferers could number as high as 4.78 million; that number is expected to quadruple by the year 2050 (Brookmeyer, & Gray, 2000).

Despite medical advances and various forms of public health assistance, the increase in the number of the elderly dependent on others for assistance will continue to increase, straining already limited individual and societal resources (Kunkel & Applebaum, 1992; U.S. AOA, 1999a; Vedhara, Bennett, Clark, Lightman, Shaw, Perks, Hunt, Philip, Tallon, Murphy, Jones, Wilcock, & Shanks, 2003; Vedhara, Cox, Wilcock, Perks, Hunt, Anderson, Lightman, & Shanks, 1999). Alzheimer's disease and related disorders (ADRD) incur an economic toll of approximately \$100 billion per annum in the United States alone (U.S. General Accounting Office, as quoted in Wisnieski, Belle, Coon, Marcus, Ory, Burgio, Burns, & Schulz, 2003).

Dementia caregiving

As the prevalence of dementia increases, so do the physical, psychological, and economic costs of dementia care (Garand, 2000). The vast majority of persons with dementia reside in the community, able to do so because of the care received from their families. Indeed, estimates of those dementia patients receiving care at home by a family member run as high as 66% (Able, 1987; Day, 1985; Doty, 1986; Rockefeller, 1991). The Advisory Panel on Alzheimer's research has recommended that current research emphasize services that reduce the burden of care for familial ADRD caregivers (Advisory Panel on Alzheimer's Disease, 1993) and that research focus on implementation and evaluation of interventions aimed at family caregivers (Advisory Panel on Alzheimer's Disease, 1993).

Caregivers dealing with the symptoms from gradual, progressive, irreversible neurodegenerative disease such as ADRD in their relatives or spouses witness

progressive loss of memory, possible behavioral disturbances, deterioration of executive function, language and motor deficits, and altered personalities (American Psychological Association, 2000). The rate of decline, and general course of the illness are unpredictable; the only sureties are an ever-increasing need for caregiving (both in time and intensity) and eventual death of the patient. As the disease course progresses, caregiving becomes a 24/7 job, with the average length of the illness from onset of symptoms to death between 8-10 years (American Psychological Association, 2000), and the range from 2-20 years. Given the progressive and irreversible nature of dementia, as well as the behavioral and emotional changes that accompany disease progression, the personality of the patient often changes drastically; frequently to the point where the patient bears little to no resemblance behaviorally to his/her former self. In a familial caregiving environment, this transformation in the patient often changes the nature of the established relationship between the caregiver and the care recipient. In fact, caregivers often report unresolved grief, in that the family member they once knew is gone, but the reminder of who they once were is present on a daily basis.

Isolation of the caregiver also occurs, as friends stop visiting and the demands of caregiving curtail or eliminate social activities. Financial resources become strained as the cost of household modifications, assistive devices, special food, and time lost at work continue to mount. Day (1985) estimates that about 1/3 of all households providing dementia care do so at the demand level of a full-time job. Day (1985) also believes the cost of government and private sector services to the institutionalized and community dwelling elderly is exceeded by the monetary value of the services provided by familial

ADRD caregivers. Putting a number on those services, U.S.AOA (1999a) has estimated that family caregivers save the U.S. health care system \$196 billion per year.

The spouse is most often the primary caregiver (Grant, et al, 2002; Schulz & O'Brien, 1994), with numbers of spousal caregivers estimated to be between 2.4 and 3.1 million and expected to rise dramatically as the population ages (Schulz & O'Brien, 1994; U.S. AOA, 1999a; Wisniewski et al., 2003). In addition to the caregiving difficulties described above, the underbelly of the problem for spousal caregivers is that they are often elderly themselves, are at an increased risk for injury, illness, and they face an exacerbation of already declining immune system function (Grant, et al, 2002; Padgett, Dobbs, & Sheridan, 2000; Robinson-Whelen, Kiecolt-Glaser, & Glaser, 2000; Schulz & O'Brien, 1994). Interestingly, Kiecolt-Glaser and Glaser (1999a) feel that spouses are at a "unique disadvantage" (p. 2259) when compared to other caregivers, due to the loss of the central relationship (marriage) and support system of their lives. They state "the prime source of support can become a major generator of stress, while simultaneously limiting the partner's ability to seek support in other relationships" (p. 2260). Hawkley and Cacioppo (2004) echo that belief when they state "the most stressful experiences that people endure are typically those that strain or break social connections" (p115). Indeed, Schulz and Beach (1999) found that among older spousal caregivers reporting caregiving strain, the risk of all-cause mortality was 63% greater than in non-caregiving controls.

Thus, the cumulative strain of caregiving over an extended period of time has the potential to impact the immune system with the weight of a chronic stressor, in conjunction with the age-related decline of immune system function (immunosenescence). Additionally, there is a substantial body of research that supports the correlation between

dementia caregiving and elevated levels of caregiver depression (Dura, Stukenberg, & Kiecolt-Glaser, 1991; Schulz, O'Brien, Bookwala, & Fleissner, 1995), distress (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991), and perceived burden (Schulz, Visintainer, & Williamson, 1990; Wisniewski, Belle, Coon, Marcus, Ory, Burgio, et al., 2003).

Psychological stress and Immune function

There is an impressive body of evidence that connects immune down-regulation and psychological stress (Kiecolt-Glaser, McGuire, et al., 2002). Substantive effects linking psychological stress and immune system down-regulation have been found in diverse and varied areas, such as cancer (Fawzy, Fawzy, Hyun, Elashoff, Guthrie, Fahey, et al., 1993), HIV (Kemeny, 1994; Kemeny, Weiner, Duran, Taylor, Visscher, & Fahey, 1995), wound healing (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998), autoimmune diseases (Ackerman, Martino, Heyman, Moyna, & Rabin, 1998), infectious diseases (S. Cohen, Frank, Doyle, Skoner, Rabin, & Gwaltney, 1998), discordant close relationships (Kiecolt-Glaser, Glaser, Cacioppo, MacCallum, Snydersmith, Kim, et al., 1997), personality and coping styles (Segerstrom, 2000),

Additionally, links between psychological stress and immune down-regulation have been found in laboratory models of stress (Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992), short term (acute) stressors (Glaser, Kiecolt-Glaser, Malarkey, Kennedy, & Hughes, 1992), and long-term (chronic) stressors (Dekaris, Sabioncello, Mazuran, Rabatic, Svoboda-Beusan, Racunica, et al., 1993).

Caregiving and other chronic stressors have a wide variety of health risks associated with them, and distress-related immune dysregulation is suspected of being one central mechanism behind those health risks (Kiecolt-Glaser, Preacher, et al, 2003).

Psychological stress, immune function, and ADRD caregivers

Of particular interest, and the focus of this study, were the links between psychological stress and immune system down-regulation that have been found among the familial caregivers of ADRD patients (Castle, Wilkens, Heck, Tanzy & Fahey, 1995). Studies have compared spouse caregivers of stroke or dementia victims to noncaregivers and found both male and female caregivers have: poorer immune responses to pneumonia and pneumococcal vaccines (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Glaser, Sheridan, Malarkey, MasCalum, & Kiecolt-Glaser, 2000; Vedhara, Cox, Wilcock, Perks, Hunt, Anderson, et al., 1999); a higher number of infectious illness episodes (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991); delayed wound healing (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995); greater risk for coronary heart disease (Vitaliano, Scanlan, Zhang, Savage, Hirsch, & Siegler, 2002); and have greater risk for developing hypertension (Shaw, Patterson, Ziegler, Dimsdale, Semple, & Grant, 1999; Grant, Adler, Parrerson, Dimsdale, Ziegler, & Irwin, 2002).

Immune System Function

As most readers of this dissertation are psychological professionals without specialized training in the field of immunology, a brief description of immune system functioning is herein provided. This writer would ask the reader to bear with this description, as substantial sections of the dissertation will not be intelligible unless this

information is provided. As the reader may expect to be unfamiliar with a number of terms used in describing and discussing immune system functions, a glossary is provided (see Appendix A) for ease of reference.

The immune system is reasonably conceived of as functioning as a sensor (Blalock, Smith, & Meyer, 1985; Maier & Watkins, 1998) responding to cells foreign to the body, and differentiating between self and non-self on a cellular and molecular level. Any immune response involves two factors: recognition of a pathogen or other material foreign to the body, and response, i.e., a reaction to eliminate the invader (Roitt, Brostoff, & Male, 1993). There are two general types of immunity: innate (non-adaptive) and acquired (adaptive). The difference between the two types of immunity is that the adaptive response is very specific for a particular antigen (antibody generators), and is a remembered response, improving in each encounter with the infectious agent thus preventing future infection (e.g., vaccination, measles). It should be noted that the specific immune response is a slow process, with an antibody to a specific antigen unable to be detected for about 3-4 days after entry into the body (Maier & Watkins, 1998). This implies that the initial immune response to infection cannot be specific (Maier & Watkins, 1998).

The key features of the acquired immune response are memory and specificity (Roitt, Brostoff, & Male, 1993). Memory enables the specific immune response to be much more rapid the second time an antigen is encountered (Maier & Watkins, 1998). In contrast, innate immunity is non-specific, does not require a prior encounter with a pathogen to function, is genetically determined, and present at birth. It involves the actions of the phagocytes (see below), which respond to a general feature of “nonself”.

Innate immune response is typically rapid, with a detectable response occurring within 1-2 hours after foreign substance entry into the body. Most immune responses are initially innate, then become more adaptive in nature (Roitt, Brostoff, & Male, 1993; Maier & Watkins, 1998; Miller, 1998).

Two general types of cells divide the work of the immune system: lymphocytes (white blood cells), which are specialized cells for the recognition of foreigners; and monocytes/macrophages (mononuclear phagocytes), whose primary function is the “eating” of other cells (phagocytosis). Additionally, macrophages can also respond to the products released by injured “self” cells, and can synthesize and release proinflammatory cytokines (see below) (Cohen, H.J., 1997; Roitt, Brostoff, & Male, 1993; Maier & Watkins, 1998).

The lymphocytes mount a specific response to antigens (antibody generators), which are the “non-self” structures presented by other cells. Examples of antigens are a virus, allergen, or a bacterium (Kiecolt-Glaser & Glaser, 1995). Lymphocytes specifically respond to antigens presented by other cells associated with 2 classes of proteins known as major histocompatibility complex (MHC I & II). Simply, the immune system strategy is to recognize antigens and arrange for their removal or destruction by phagocytes.

The central lymphoid tissues are the thymus and the bone marrow, and these comprise the two major arms of the immune system, the cellular and the humoral. Additional organs involved in immune system function are the lymph nodes, spleen, tonsils and adenoids, and Peyer’s patches, located in the small intestine (Kiecolt-Glaser & Glaser, 1995).

There are three subtypes of lymphocytes: B-lymphocytes, T-lymphocytes, and the natural killer (NK) cell. The B-lymphocytes are produced in the bone marrow, and are part of the humoral arm of the immune system. They are responsible for production of antibodies or immunoglobulins-serum proteins. When stimulated by antigen, they mature into plasma cells that synthesize humoral antibody with remarkable specificity (Roitt et al., 1993; Kiecolt-Glaser & Glaser, 1995).

In the case of antibodies, there are five major classes. IgG, or immunoglobulin G, is the most abundant antibody in the blood, and the only class of antibodies that can cross the placental barrier from mother to fetus, thus providing the newborn with a primary defense against disease. IgM is the first antibody to appear in the blood after exposure to a new antigen, and is replaced by IgG after a week or two. IgD is another form of antibody; the precise function is currently unknown, but it may play an important role in antigen-triggered lymphocyte differentiation. IgA is the most important antibody in saliva, tears, genital, urinary, and intestinal fluids. It forms the first line of defense against organisms attempting to gain access to the body through mucous membranes. Lastly, IgE attaches to mast cells, and releases mediators responsible for the production of the symptoms of allergies. It is an important line of defense against parasites and worms (Cohen, H.J., 1997; Cohen, H.J., 2000). Overall, defense against bacteria and viruses in body fluids is a particular focus of the immune response of the humoral branch.

Cells that mature in the thymus are known as T-lymphocytes (T-cells), and make up the cellular, or non-antibody-producing arm of the immune system. Each T cell has receptors that enable it to bind to, or recognize, a single antigenic site, and only a very small number of T cells can recognize the same antigenic site. This property of T cells,

and the need for T cells to recognize a phenomenal diversity of antigenic sites, demands that there be a corresponding diversity in the population of T cells. Estimates for the amount of different T cells in the human body are in the one million range (Maier & Watkins, 1998).

Functionally, T-cells move around the body and can kill such target cells as intracellular viruses, fungi and yeast infections, intracellular bacteria such as tuberculosis, cancer cells, and graft or transplant tissue (Cohen, H. J., 1997; Kiecolt-Glaser & Glaser, 1995). T-cells examine cell surfaces for mutations or abnormalities, and respond to cell surface-associated antigens. T-cells fall into one of three functional varieties: Cytotoxic T-cells; helper T-cells, and suppressor T-cells.

Cytotoxic T-cells (CD4+ cells) travel to an invasion site in the body, and lyse (lysis; dissolution, destruction or decomposition of cells) antigen bearing cells by producing cytotoxic factors that destroy the cells (Garand, 2000; Kiecolt-Glaser & Glaser, 1995). Helper T-cells stimulate B-lymphocytes to produce antibody, carry out delayed hypersensitivity reactions, and secrete cytokines (also called lymphokines, discussed in more detail below) which encourage both the proliferation and differentiation of T, B, and other cells. It is important to note that there are two subsets of helper T-cells (Th1 & Th2) that have the potential to control the cellular immune response (Th1) and the humoral immune response (Th2). These helper T-cells respond to antigens associated with MHC II, while the cytotoxic T-cells respond to antigens associated with MHC I (Garand, 2000; Cohen, H.J., 1997; Cohen, H.J., 2000).

Suppressor T-cells (CD8+) balance the action of the helper T-cells, and serve to inhibit the immune response, shutting off helper T-cells when sufficient antibody has been produced (Kiecolt-Glaser & Glaser, 1995).

The third lymphocyte sub-type is the natural killer cell (NK). NK cells mature in the bone marrow, and do not require prior exposure to a direct antigenic stimulus. Thus, they are able to kill target cells in a non-specific manner. NK cells defend against viruses and cancer, and are essential in the prevention of tumor growth and cancer metastases, forming a type of anti-tumor surveillance system (Garand, 2000; Kiecolt-Glaser & Glaser, 1995).

Cytokines and Immune Function

Of particular importance in this study were the cytokines (lymphokines). Cytokine is simply a generic term for soluble protein molecules that mediate interactions between cells. Secreted by helper T-cells, they help control immune responses (Roitt, Brostoff, & Male, 1993). Two broad groups of cytokines are the interferons (IFNs) and the interleukins (ILs), which are essential chemical mediators of various aspects of immune function (Kiecolt-Glaser & Glaser, 1995).

The specific cytokines of interest were the pro-inflammatory cytokines (interleukin-6, IL-6; interleukin 1-beta, IL-1 β ; and tumor necrosis factor alpha, TNF α). These are all proteins with local effects such as inflammation and attraction of other immune cells to assist in healing at a wound site. Significantly, the pro-inflammatory cytokines also act globally, coordinating widespread, complex changes throughout the body that are designed to combat injury and infection. This is known as the acute-phase response

(Baumann & Gauldie, 1994). Some of those physiological changes include fever, increased slow-wave sleep, changes in liver protein synthesis, and an increase in the levels of circulating white blood cells (leukocytosis). Those complex changes are not restricted to physiology; behavioral changes can occur such as reductions in social interaction, aggression, sexual behavior, general activity, exploration, and increased responsiveness to pain (Kent, Bluthé, Kelley, & Dantzer, 1992). Mood changes such as depression (Hart, 1988) and cognitive disturbances, such as loss of attention and certain types of memory (Aubert, Vega, Dantzer, & Goodall, 1995) have been described as well.

Additionally, activation of the sympathetic nervous system (SNS), sometimes described as a “classic stress response” (Maier & Watkins, 1998), can occur leading to release of epinephrine and norepinephrine (plasma catecholamines) and activation of the HPA axis. This in turn leads to the release of adrenocorticotrophic hormone (ACTH), which subsequently stimulates the release of glucocorticoids (Dunn, 1995; Maier & Watkins, 1998).

Interleukin-6

As a group, the proinflammatory cytokines have been implicated in the onset and course of a number of age-associated diseases, such as general frailty and functional decline, Alzheimer’s disease, periodontal disease, osteoporosis, arthritis, type 2 diabetes, cardiovascular disease, as well as certain cancers (Kiecolt-Glaser, Preacher, MacCallum, Atkinson, Malarkey, & Glaser, 2003).

Of the proinflammatory cytokines, IL-6 was the central focus in this study and IL-6 plasma concentration levels constituted one of the dependent variables. There are several reasons for the choice of IL-6 as a dependant variable: the role of IL-6 in inflammation;

the association of inflammation with the aging process (this becomes especially significant when considering that the vast majority of ADRD caregivers are elderly); the increase of serum levels of IL-6 with age; and the remarkable increase in circulating levels of IL-6 in ADRD caregivers as compared to non-caregivers. The following section will give detail to the above listed reasons.

IL-6 is produced by monocytes and macrophages, as well as mast and endothelial cells, and is responsible for a number of aspects of immune regulation, especially through its central role in inflammation. While most cytokines reach biologically effective concentrations at the site of inflammation, IL-6 is a major circulating cytokine typically produced in response to infection and/or inflammatory insult (injury). It is a profound stimulus for production of hepatic (liver) acute phase proteins, induction of fever, and activation of the hypothalamic-pituitary-adrenal (HPA) axis (Smith, et al., 2004).

The serum concentration levels of IL-6 are known to increase with age (Ershler, 1993; Daynes, Araneo, Ershler, Maloney, Li, & Ryu, 1993), and have been implicated in the processes of normal aging and age-related conditions (Lutgendorf, Garand, Buckwalter, Reimer, Hong, & Lubaroff, 1999). In fact, one of the fundamental aging processes may be changes in IL-6 regulation (Koenig, et al., 1997). Due to the fact that inflammation is a component of many age-associated chronic diseases which often cause disability, high circulating levels of IL-6 may contribute to functional decline in old age (Ferrucci, Harris, Guralnik, Tracy, Corti, Cohen, et al., 1999).

Depression, frequently associated with the caregiving experience (Cook, Pearson, & Ahrens, 1997; Levesque, Cossette, & Laurin, 1995); chronic stress experiences, of which dementia caregiving is known to be one (Kiecolt-Glaser, Dura, Speicher, Trask, &

Glaser, 1991; Kiecolt-Glaser, Preacher, et al., 2003); post-traumatic stress disorder (PTSD; Maes, Lin, Delmeire, Van Gastel, Kenis, De Jongh, et al., 1999) and other negative emotions can directly stimulate the production of IL-6, as well as other pro-inflammatory cytokines (Dentino, Pieper, Rao, Currie, Harris, Blazer, et al., 1999; Maes, Bosmans, De Jongh, Kenis, Vandoolaeghe, & Neels, 1997; Lutendorf, Garand, Buckwalter, Reimer, Hong, & Lubaroff, 1999; Maes, Song, Lin, De Jongh, Van Gastel, Kenis, et al., 1998).

Circulating levels of IL-6 have been found to increase at a rate 4 times greater in familial ADRD caregivers than in matched controls (Kiecolt-Glaser, Preacher, et al., 2003). Female Alzheimer caregivers had significantly ($p < .005$) higher IL-6 levels than three noncaregiver groups (Lutendorf, Garand, Buckwalter, Reimer, Hong, & Lubaroff, 1999). Additionally, peak plasma IL-6 concentration has been significantly correlated ($p < 0.006$) with stroke severity 5 to 7 days post event ($r = .54$) and clinical outcome at the 3 month and 12 month mark ($p = 0.001$, $r = -0.64$), ($p = 0.003$, $r = -0.63$) (Smith, et al., 2004).

On other physiological fronts, IL-6 has attracted attention due to its central role in promoting the production of C-reactive protein (CRP). CRP has been identified as an important cardiac risk factor, and in apparently healthy males, high concentrations of CRP have predicted the risk of future cardiovascular disease (Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). More recent studies (Lee, Hill, Walley & Frolich, 2006; McDade, Hawkey, & Cacioppo, 2006) support CRP as a consistent, although “moderate” predictor of cardiovascular events in both healthy and diseased populations. In the Lee et al. study, elevated levels of IL-6 emerged as the most robust predictor of

cardiac hazard. The presence of elevated levels of CRP and IL-6 has been implicated in more than cardiovascular disease. Additionally, diseases associated with disability such as osteoporosis, arthritis, congestive heart failure, and stroke have been tied to pathogenic roles for IL-6 and CRP (Ferrucci, et al., 1999; Smith, et al., 2004).

Measures of Immune Function: Immune system assays

This section briefly describes some of the assays more commonly used in assessing immune system functioning, and will assist the reader in understanding results discussed in the following literature review section covering studies using immune system measures.

There is no single immunological assay that provides a global measure of immune system function (Kiecolt-Glaser & Glaser, 1995a). Typically, immunological assays are divided into two distinct categories: functional assays, which reflect the functional efficacy or performance of cells; and enumerative assays, which provide information on numbers or percentages of cells. It should be noted that cell function and cell number are not necessarily correlated (Kiecolt-Glaser & Glaser, 1995a). Comparing the two types of assays and psychosocial stressors, the correlation is stronger and more reliable with functional assays (Kiecolt-Glaser & Glaser, 1991). In studying older populations, functional assays are viewed as essential (Kiecolt-Glaser & Glaser, 1995a).

Types of functional assays

Blastogenesis is the proliferative response of lymphocytes to stimulation by mitogens (substances used in the laboratory that have the ability to stimulate lymphocyte proliferation or replication). When used *in vitro*, the proliferation of T and B-

lymphocytes in response to such stimulation is thought to provide a model of the body's response to infectious challenge. Common mitogens (see glossary) used are phytohemagglutinin (PHA; stimulates T cells); pokeweed (PWM; stimulates both T and B cells); and concanavalin A (Con A; a T cell mitogen) (Reinherz & Schlossman, 1980).

Blastogenesis typically involves lymphocyte incubation with a mitogen using a radioactive isotope. Cell division (proliferation) can then be quantified by measuring incorporation of radiation. One of the few immunological assays to be reliably associated with meaningful health parameters, reduced blastogenesis (i.e., lymphocyte proliferation) reflects immune function down-regulation such as occurs in AIDS, other less severe illnesses, and normal aging (immunosenescence) (Kiecolt-Glaser & Glaser, 1995a).

Natural killer (NK) cell activity is another common functional measure of immune activity. The ability of NK cells to lyse (destroy) target cells, typically tumor cells, is measured by growing target cells in a medium incorporating a radioactive isotope; when NK cells are introduced into the medium they lyse the target cells. The efficacy of lysis is determined by measuring the amount of isotope released (Kiecolt-Glaser & Glaser, 1995a). In their meta-analysis of stress and immunity in humans Herbert and Cohen (1993a; 1993b) found a moderate to large effect size in a number of depression or stress studies measuring NK cell activity.

Latent herpesvirus antibody titers have shown the "most consistent relationships to psychosocial variables of any of the diverse immunological assays (we have) used in our laboratory" (Kiecolt-Glaser & Glaser, 1995a; p. 219). This functional assay is based on the principles of acquired immunity (see above), with the immune system "remembering"

pathogens previously encountered. Vaccination is based on the principle of immunological memory. Interestingly, some viruses (HIV, herpesvirus) can actually hide in a latent state inside specific host cells. Once infected, individuals remain latently infected for life, and cellular immune system competence is thought to be critical in controlling the primary, as well as the latent, herpes infection (Kiecolt-Glaser & Glaser, 1995a). Thus, decreased cellular immune system competency is reflected in higher, rather than lower, levels of antibody titers to the latent herpesvirus, and reliable changes in those levels have been shown in response to psychosocial stressors (Glaser & Kiecolt-Glaser, 1994, 1998; Kemeny, et al., 1995; Kiecolt-Glaser, Ricker, et al., 1984; Kiecolt-Glaser, Malarkey, et al., 1993).

Interleukin-6, the immunological variable of interest in this study, has been detailed in a previous section. While it might be described as a type of enumerative assay in that levels of IL-6 are being measured, the research cited in the previous section has established the validity of IL-6 as a measure of immune function, especially in an aged population. To briefly review, serum levels of IL-6 are known to increase with age; IL-6 has been implicated in the processes of normal aging, age-related conditions, and functional decline; IL-6 production may be stimulated by chronic stress and negative emotions such as depression; and circulating levels of IL-6 have been found to increase at a rate 4 times greater in familial ADRD caregivers than in matched controls.

The levels of IL-6 in humans are commonly assayed with commercially available enzyme-linked immunosorbent assay (ELISA) kits. Blood samples are typically drawn in the morning within a narrow specified window of time to avoid circadian changes in IL-6 levels. Blood is then cooled, centrifuged at the lab, and the plasma kept frozen at between

40-70⁰C until thawed for analysis using the ELISA kit. Samples are all run the same day, single run, with a single lot number of reagents (substance employed to produce a chemical reaction) and consumables by a single operator (Lutgendorf, et al., 1999; Maes, Lin, Delmeire, Van Gastel, Kenis, De Jongh, & Bosmans, 1998; Smith et al., 2004; Suarez, 2003).

Models of Immune function

The previous sections have outlined the conceptual framework (in an immunological sense) basic to this dissertation. This section continues to lay the theoretical underpinnings for this study by briefly describing two primary models for suppression of immune system functioning: the immunosuppressive model, and the glucocorticoid-resistance model.

Immunosuppressive model

The relationship between stress, immunity, and disease has been described as the immunosuppression model. The foundational tenet of the model is that the risk for adverse health outcomes is heightened by the stress-related suppression of the immune response in such a way that the host is left vulnerable to opportunistic disease (Miller, Cohen, Ritchey, 2002). While the precise mechanism or pathways by which stress downregulates immunity is not known, there are three probable components to the process: (1) downregulation occurs in part by activation of the autonomic nervous system fibers that descend from the brain to the lymphoid organs (Felton & Felton, 1994); (2) by triggering the secretion of neuropeptides and hormones that bind to white blood cells and alter their function (Blalock, 1994); (3) inducing self-medicating and immunomodulatory

behaviors, such as alcohol consumption and cigarette smoking (Kiecolt-Glaser & Glaser, 1988). Taken in sum, the result is a diminished immune capacity to effectively respond to challenge (Anderson, Kiecolt-Glaser & Glaser, 1994; Cohen & Williamson, 1991).

The immunosuppressive model does a good job in explaining the heightened risk for negative health outcomes due to stress compromised host resistance. However, the model has an important limitation in that it is unable to parsimoniously explain the influence of stress on various diseases whose core feature is inflammation (Miller, Cohen, Ritchey, 2002). Inflammation is a major player in the pathogenesis of rheumatologic, autoimmune, allergenic, cardiovascular diseases, as well as being implicated in the process of normal aging and disability; all of these conditions seem to be exacerbated by chronic stress (Harris, Ferrucci, Tracy, Corti, Wacholder, Ettinger, et al., 1999; Kiecolt-Glaser & Glaser, 1999a; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). However, in contrast to the research involving chronic stress and inflammation, the immunosuppressive model would predict that stress should improve disease resistance by suppression of the inflammatory response. The weight of the research does not support this prediction (Miller, Cohen, Ritchey, 2002). However, there is evidence that acute stress can, under certain circumstances, enhance immune system function, and that chronic stress is quite often deleterious in its immune effects (Dhabhar & McEwen, 1997; Miller et al., 2002; Maier & Watkins, 1998).

Glucocorticoid resistance model

The glucocorticoid-resistance model focuses on hormones critical to the termination of the normal immune inflammation response. Its foundational premise is that immune system sensitivity to glucocorticoid hormones (such as cortisol) is diminished by chronic

stress. This diminished sensitivity in turn then decreases the immune system's ability to terminate the inflammatory cascade caused by the interleukins (Miller, Cohen, Ritchey, 2002). The model is based on the idea that the secretion of the hormonal products of the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes are stimulated by chronic stress. In time, continued exposure to high concentrations of these hormones engenders a counterregulatory response from the white blood cells by downregulating the expression and/or function of the glucocorticoid hormone receptors (Maier & Watkins, 1998; Miller, Cohen, Ritchey, 2002).

Three assumptions provide a basis for the models' validity. First, stressful circumstances can stimulate ongoing secretion of hormones from the HPA and SAM axes. As perceived demand outstrips or outpaces perceived ability to cope and/or personal resources, the physiological consequence is that the body's output of cortisol, epinephrine, and norepinephrine increase. Several studies have yielded support for this assumption (Baum & Grunberg, 1995; Kirschbaum & Hellhammer, 1989; Weiner, 1992). However, it should be noted that this is not always the case. In some patients with post-traumatic stress disorder (PTSD), epinephrine and norepinephrine are consistently elevated; however, cortisol secretion is consistently blunted (Yehuda, 2000).

The glucocorticoid-resistance model's second assumption is that cortisol is the central player in the regulation of the inflammatory response to infection and injury. In support of this assumption, animal studies with rodents have shown that disruption of the HPA axis predisposes the rodents to chronic inflammatory illness. Interestingly, the illness resolves through restoration of the hormonal pathways by administration of

synthetic glucocorticoids (Chrousos, 1995; Sternberg, Hill, Choursos, Kamilaris, Listwak, Gold, & Wilder, 1989; Sternberg, Young, Bernardi, Calogero, Chrousos, Gold, & Wilder, 1989). The third and final assumption of the model is that glucocorticoid receptors are downregulated and immune system sensitivity to cortisol declines as a result of prolonged exposure to hormones. In vivo support for this assumption comes from clinical studies of inflammatory disease showing that long-term administration of synthetic glucocorticoid medications (such as dexamethasone) induces a glucocorticoid-resistance syndrome such that dosages initially therapeutic fail to offer much relief, not unlike the phenomenon of tolerance in certain drugs of abuse (Chrousos, Detera-Wadleigh, & Karl, 1993; DeRijk & Sternberg, 1997; Leung, De Castro, Szefer, & Choursos, 1998).

In summary, the glucocorticoid-resistance model does not argue that the immune system becomes completely unresponsive to glucocorticoids as a result of a chronic stress-induced syndrome; it does, however, argue that the immune system's glucocorticoid sensitivity will be diminished by stress to some extent. This in turn facilitates the "continued expression of pro-inflammatory cytokines following infection and/or injury" (p. 538; Miller, Cohen, Ritchey, 2002). Recent research (Geiss, Rohleder, Anton, 2006) with fibromyalgia patients showed a reduced feedback sensitivity of the HPA axis indicated by reduced glucocorticoid suppression in the morning hours, and a 400% increase in IL-6 response after measurement of their pressure pain thresholds at tender point sites.

Essentially, the glucocorticoid-resistance model describes an identifiable pattern of immune system changes that accompany chronic stress.

The Brain and the Immune system

The previous sections have outlined support for the chronically stressful nature of dementia caregiving, immune system function, and immune consequences of exposure to chronic stress in general, including the stress of spousal dementia caregivers. We have also briefly examined two models of immune system suppression: the immunosuppression model, and the glucocorticoid-resistance model. The next section will examine the relationship between brain and immune system functioning, building on the information presented in the previous sections. This relationship is critically important for this reason: the argument, and the weight of the evidence presented, propose that environmental events characterized as stressors activate the same neural circuitry as that activated by infectious agents. But, as already described, infectious agents physically contact macrophages and other cells and activate them on the basis of such contact. A stressor cannot do that; yet the overwhelming weight of the evidence indicates that a psychological stressor has distinct physiological consequences. The question remains: how does this occur? The following section proposes an answer to that question.

Research suggests that the relationship between the brain and the immune system constitutes a complex, bi-directional communications network. Nerve endings in the spleen, bone marrow, thymus, and lymph nodes have been found (Adler, 1983; Kelly, 2004; Maier & Watkins, 2003). Also, there are specific receptor sites for IL-1, IL-6, and TNF in the brain (Cunningham & de Souza, 1993; Maier & Watkins, 1998).

In this network, the immune system functions as a diffuse sense organ, providing information to the brain about various events in the body (Blalock, Smith, & Meyer,

1985; Maier & Watkins, 1998). Clearly, the proinflammatory cytokines (IL-1 β , IL-6, and TNF α) secreted by T-cells, macrophages, and other immune system cells communicate with the brain and alter neural activity (Maier & Watkins, 1998). How then does this communication occur? The most obvious answer is that they accumulate in the blood, and travel to the brain via the bloodstream, crossing the blood-brain barrier (BBB) in the process. However, the proinflammatory cytokines are relatively large lipophobic (fat avoiding) molecules and most unlikely to be able to cross the BBB, as the extracellular space of the CNS is impermeable from the blood to even extremely small molecules (Maier & Watkins, 1998). In fact, the BBB hinders the passage of antibodies and other immune system substances into the brain; thus, the mechanisms to counter infection in the brain are less effective than those functioning elsewhere in the body (Reitan & Wolfson, 1992).

However, some researchers (Banks, 2001; Blatteis, 1992; Rivest, 1999) argue that there are potentially three specialized mechanisms for allowing blood-borne cytokines entry into the brain: (1) active transport; (2) crossing at circumventricular organs, where the BBB is absent or weak; (3) binding to receptors within the cerebral vessels. Recently, using an in vitro model of mouse brain endothelial cells (which make up the blood-brain-barrier-BBB), Verma, Nakaoke, Dohgu, & Banks (2006) obtained results that supported the BBB as an important source of cytokines, confirming the secretion of Interleukins (including IL-6) from the BEC's. They concluded that the BBB can release cytokines from one side of the neuroimmune axis into the other in response to immune challenges.

It is a certainty that each of these mechanisms operates to transport a cytokine signal from the periphery to the brain (Maier & Watkins, 2003). However, in the case of

infection that does not result in measurable blood levels of cytokines, but neurally mediated sickness responses (acute-phase response; see Glossary) nevertheless occur, another mechanism may be at work (Maier & Watkins, 1998).

Some researchers (Fleshner, Goehler, Hermann, Relton, Watkins, & Maier, 1995; Maier, Groehler, Fleshner, & Watkins, 1998; Maier & Watkins, 1998; Maier & Watkins, 2003) have suggested that cytokines communicate to the brain via the vagus nerve. Recent research has expanded the understanding of vagal function; while the vagus nerve has been traditionally viewed as primarily an efferent nerve responsible to provide parasympathetic input from the brain to the visceral organs, the current understanding is that approximately 70% of the vagal fibers are in fact sensory. These afferent fibers are responsible for sending messages from the innervated organs to the brain (Maier & Watkins, 1998; Watkins & Maier, 2000). While interleukin receptors have not been found on the vagus, dense concentrations of binding sites for IL-1 have been found on paraganglia that surround and innervate vagal fibers (Maier & Watkins, 1998; Maier & Watkins, 2003).

If the vagus does indeed carry afferent messages from the peripheral immune system to the brain, then severing the vagus reduces or eliminates sickness response to immunogenic stimuli. Research supports this hypothesis, with fever (Watkins, Maier, & Goehler, 1994), hyperalgesia (Watkins, Wiertelak, Goehler, Mooney-Heiberger, et al., 1994), glucocorticoid increases (Fleshner, et al, 1995) and conditioned taste aversions attributed to cytokines no longer occurring.

Classic Stress Response

The previous sections have described immune system function, models of immune system dysfunction, and bi-directional immune-brain communication. The majority of the information has focused on cellular level function; a last brief word needs to be said on the functioning of two interrelated systems viewed as the primary indicators of the stress response, the HPA axis and the SAM axis. Both axes are activated by the central nervous system (CNS) in response to stressors, with specific biochemical cascades (Garand, 2000; Miller, et al., 2002) and consequences, one of which is dysregulation of cytokine production (Glaser & Keicolt-Glaser, 1998; Maes et al., 1998). The response of both systems is usually stereotypic and widespread bodily manifestations of the flight-or-fight response (Beatty, 2001).

Sympathetic-Adrenal-Medullary (SAM) Axis

The SAM axis is thought to be the first system activated during acute stress. It is primarily involved in arousal, attention, and associated with enabling an adaptive advantage during stressful situations. It is the primary contributor to the “fight or flight” reaction, and activation results in the release of catecholamines (epinephrine, norepinephrine) from the adrenal medulla and sympathetic nerve endings into the bloodstream. This results in increased heart rate, blood pressure, glucose production, and pupil dilation, as well as decreased blood flow to the gastrointestinal tract (Beatty, 2001).

Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis is considered to be the second wave of the human stress response, is generated by the endocrine system, and is slower and longer acting than the SAM response (Beatty, 20001). The paraventricular nucleus of the hypothalamus (PVN),

located on the sides of the third ventricle, produces the endocrinological stress response (Maier & Watkins, 1998; Beatty, 2001). The perception of a stressor by the brain triggers secretion of corticotropin-releasing hormone (CRH) into the pituitary. CRH secreted by the PVN is the primary integrating peptide for the stress response (Beatty, 2001; Maier & Watkins, 1998; Yehuda, 2003). The anterior pituitary then releases adrenocorticotrophic hormone (ACTH) into general circulation, where it travels to the adrenal cortex and stimulates release of steroid hormones (glucocorticoids, i.e., cortisol) into the bloodstream. (Beatty, 2001; Garand, 2000).

Glucocorticoids are extremely catabolic (they can be anabolic as well), causing shifts in carbohydrate metabolism, breakdown of lipids, sugars, and proteins for energy in support of strenuous physical activity; increasing cardiovascular tone, altering cognition, inhibiting growth, immune, and inflammatory responses; all responses critical to adaptation to acute physical stress (Beatty, 2001; Garand, 2000; Sapolsky Krey, & McEwen, 1986). However, prolonged exposure to glucocorticoids (as in the case of chronic stress) can lead to immunosuppression, hypertension, steroid diabetes and infertility (Moynihan, 2003; Sapolsky, et al. 1986). Ultimately, the inability to cease glucocorticoid secretion at the end of a stressor may be as damaging as the inability to initiate it at stressor onset (Maier & Watkins, 1998; Moynihan, 2003; Sapolsky, et al. 1986).

Model of Stress

There has been considerable mention made in this chapter of stress, acute stress, chronic stress, and distress. For the purposes of this study, stress and distress were

considered synonymous. The next chapter reviews a number of studies on important aspects of stressor type, duration, and frequency. In this context, then, how was stress operationalized for this study?

The word stress is used to describe a diverse array of circumstances. Hans Selye offers an acute observation when he points out that we would not use the common word “stress” to describe these diverse circumstances unless there was something common in all of them (Selye, 1980). The definition Selye formulated in 1936 was that “stress is the non-specific (common) result of any demand upon the body, be it a mental, or a somatic demand for survival and the accomplishment of our aims” (Selye, 1980). Selye subsequently developed the idea of “eustress”, which is an ideal amount of stress necessary to keep the body’s immune system in tune, but not overwhelm it. He contrasted this with “distress”, which is the type and level of stress that results in immune system compromise (Selye, 1980).

Current research supports Selye’s distinction while not using his terminology. Stressors have been found to be both a help and a hindrance to immune function (Maier & Watkins, 1998). Acute stressors (a form of eustress) have been shown to enhance immune function, while chronic stressors (distress) are seen to suppress immune function (Dhabhar & McEwen, 1997; Miller et al., 2002; Maier & Watkins, 1998). While the difference between acute and chronic stressors can be described physiologically, the psychological difference may lie in the highly idiographic area of appraisal. Differences in appraisals of an event, as well as reactions to that same event, can provoke different endocrine and immune responses (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

Thus, the type of interpretation and response rendered by the individual to the environment determines their responses to stress (Kiecolt-Glaser, et al. 2003).

The model of stress and coping proposed by Lazarus and Folkman (1984; see Appendix B) proposes that adaptation to stress is mediated by the individual appraisal of that stress, as well as the individual coping strategies employed (Kneebone & Martin, 2003). It replaces the simple stimulus-response model of stress with a stimulus-appraisal-response model (Patterson and Neufeld, 1989).

Two forms of appraisal are proposed: primary and secondary appraisal. In primary appraisal, the individual detects stress cues in the environment and evaluates the immediate relevance of danger to self. In secondary appraisal, an evaluation of the personal resources and coping options that can be brought to bear on the situation takes place. Lazarus (1978) described four primary outcomes of appraisal of any given situation: First: a neutral appraisal; analysis detects no personal relevance; no action need be taken. Second: presence of threat, an event that is thought to be uncontrollable or unavoidable. The third possible appraisal is one of loss or harm. An event has occurred with consequences for the appraiser. Fourth, challenge appraisal reveals an opportunity for harm or mastery.

Coping strategies are conceived as being of two principle types: emotion-focused and problem-focused. Emotion-focused coping is a primarily cognitive process designed to decrease emotional distress, and employs strategies such as avoidance, denial, selective attention, minimizing, and extracting positive value from negative events. Problem-focused coping strategies are similar to those used in problem solving: initially defining the problem, generating alternatives, weighing the alternative cost and benefits, choosing,

and acting. The choice of the coping strategy is viewed as dependant on the nature of the stressor.

Ultimately, the Lazarus-Folkman model views the person and environment in an interactional, “dynamic, mutually reciprocal (and) bi-directional relationship” (Kneebond & Martin, 2003; p. 2)

Summary

This section summarized the dilemmas faced by familial ADRD caregivers on a social, psychological, and physiological level. Immune system function, models of immune system dysfunction, and aspects of immune functioning particularly relevant to this study were described. Common measures of immune functioning, and their applicability were enumerated. Additionally, a bi-directional mode of brain-immune interaction was described, giving a reasonable framework for understanding the etiology of stress and immune dysregulation. Lastly, a stimulus-appraisal-response model for stress and coping was described, which was the model used for the theoretical framework for the cognitive behavioral intervention employed in the study.

The Current Study

Inasmuch as we have seen that caregivers are chronically stressed and that chronic stress may impair immune system function, the question of whether immune function protection can be provided for the caregiver naturally arises. Additionally, we have seen that IL-6 is a measure of immune system functioning, which suggests a possible means of measuring any immune system protection that might be provided.

Thus, proceeding from the theoretical base described by Lazarus and Folkman (1984), this study attempted to increase the ability to cope with the chronic stress of caregiving in familial ADRD caregivers by employing a cognitive-behavioral intervention designed specifically for that purpose and population. We measured the effects of the intervention with various psychosocial measures (described in detail in the Methods section) as well as measuring the plasma levels of IL-6. To that end, two participant groups of caregivers were recruited, and randomly divided into control and experimental groups. Measurements were collected at baseline (time 1) and 8 weeks (time 2). The questions of interest were: would there be a significant difference between the two groups on measures of IL-6 at time 2? Would there be a significant difference between the groups on the psychosocial measures at time 2? And lastly, would any particular psychosocial measures or scale on that measure emerge as a significant predictor of levels of IL-6 at time 2?

Specifically, the dependent variables measured in this study were (1) scores on the Center for Epidemiologic Studies-Depression (CES-D), producing individual and group mean scores; (2) scores on the Total Mood Disturbance (TMD) of the Profile of Mood States (POMS), producing individual and group mean scores; (3) scores on the Personal Views Survey-III-Revised (PVS-III), producing individual and group mean scores (HardiAttitudes); and (4) presence of interleukin-6 (IL-6) as measured by plasma assay, producing individual and group means results.

Study participants were expected to show a significant difference on mean scores of the CES-D, the Total Mood Disturbance (TMD) score of the POMS, the HardiAttitudes score of the PVS-III-R, and plasma IL-6 levels at the 8-week measurement between

groups, with the control group scores worsening or remaining the same from baseline measurement and the CBSM group scores remaining the same or improving from baseline measurement.

Additionally, it was predicted that there will be a significant negative correlation between mean HardiAttitudes scores on the PVS-III-R and plasma IL-6 levels at Baseline and 8 weeks in both groups and that there will be significant positive correlations between scores on the CES-D, the TMD of the POMS, and plasma IL-6 levels at Baseline and 8 weeks in both groups.

It was also predicted that there will be a significant difference between the control and intervention groups on all the POMS subscales (Anxiety, Depression, Anger, Vigor, Fatigue, and Confusion) at the 8-week measurement.

Finally, it was expected that mean HardiAttitudes scores on the PVS-III-R will be the single greatest predictor of IL-6 values at baseline and 8-weeks compared to mean scores on the TMD of the POMS and mean scores on the CES-D in both experimental and control groups.

The next chapter presents the literature reviewed that further informs the theoretical basis for this study, and the detailed hypotheses that emerged from that literature review.

CHAPTER 2

LITERATURE REVIEW

This study was an attempt to enhance immune system functioning and reduce subjective stress levels in the familial caregivers of Alzheimer's disease and related dementia (ADRD) patients. In order to accomplish this objective, a controlled comparison between a cognitively based intervention and a no-treatment control group was conducted. The unique contribution of this study to the literature was in examining the effects of a cognitive behavioral stress management (CBSM) intervention on caregiver subjective distress and caregiver immune system functioning. No other published study has examined the effect of a psychosocial intervention on caregiver stress reduction and enhanced immune function using IL-6 as a dependant measure of immune system function. This study also attempted to contribute to the existing body of knowledge in the field of psychoneuroimmunology (PNI) by addressing the complicated inter-relationship between psychological stress and immune system functioning.

The following sections provide a literature review of controlled studies investigating the efficacy of cognitive behavioral stress management (CBSM) interventions with caregivers, and supporting the efficacy of a CBSM intervention in enhancing human immune system functioning. A brief history of the research in the area

is also included. Additionally, a literature review of immune system functioning under various types of stress and of specific indicators of immune system dysfunction, in particular the proinflammatory cytokines, is included.

Stress and Immune System Changes

Duration of a stressor

Laboratory models (5-60 min)

Acute laboratory stressors that typically last one-half hour or less engender transient immune changes (Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992; Maier & Watson, 1998; Shi, Devadas, Greenelch, Yin, Mufson, & Zhou, 2003). Most immune parameters return to resting levels within 1 hour after laboratory stressors cease (Kiecolt-Glaser, et al., 1992).

Both brief and longer-term stressors are associated with declines in functional aspects of immunity (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002), but laboratory stressors seem to increase cell numbers in some lymphocyte subpopulations. In contrast, there is a decrease in lymphocyte numbers associated with longer term naturalistic stressors (Uchino, Kiecolt-Glaser, & Cacioppo, 1996). One possible mechanism is that acute secretion of stress-responsive hormones, particularly catecholamines, are capable of altering a number of aspects of immune functioning (Rabin, 1999).

In laboratory studies, both duration and intensity of psychological stressors (as indexed by cardiovascular changes) are related to the breadth and magnitude of immune changes (Benschop, Rodriguez-Feuerhahn, & Schedlowski, 1996). Immunological changes following epinephrine injections are quite similar to those observed following

short-term stressors (Schedlowski, Falk, Rohne, Wagner, Jacobs, Tewes, & Schmidt, 1993).

Short term (acute) stressors

Academic stress has been a widely used model in laboratory research (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Studies conducted over ten years of medical students' responses to examinations showed transient changes in several facets of the cellular immune response and its mediators (Kiecolt-Glaser, 1999). Data from a study done with medical students during examination cycles (Glaser, Kiecolt-Glaser, Malarkey, Kennedy, & Hughes, 1992) that looked at the student's response to a series of three hepatitis B vaccinations suggest that the immune response to a vaccine (and pathogens, by implication) can be modulated by a mildly stressful event in healthy, young adults.

Exam stress substantially interfered with the function of the immune system in wound repair, retarding the rate of repair by an average of 40% when compared to the same subjects during summer vacation (Marucha, Kiecolt-Glaser, & Favagehi, 1998).

The conclusion that academic stress, as well other common, relatively short term stressors, can provoke changes in a number of immune system functions, with associated health consequences, is supported by the above data (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). It should be noted that these changes were produced in subjects who might be considered "experts" in exam taking, and have lengthy histories of performing well under these conditions. While exams can be quite personally impactful, the fact that something as predictable, transient, and relatively benign as exam stress provokes immune changes certainly suggests that other common stressors can produce similar alterations (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

Long term (chronic) stressors

A wide variety of long-term or chronic stressors have been associated with altered immune system function. A partial listing includes burnout at work (Lerman et al., 1999) internment in a prisoner of war camp (Dekaris, Sabioncello, Mazuran, Rabatic, Svoboda-Beusan, Racunica, et al., 1993); isolation and exposure to a hostile climatic environment (Muller, Lugg, & Quinn, 1995); living near a damaged nuclear reactor (Baum, Cohen, & Hall, 1993); job strain (Kawakami, Tanigawa, Atake, Nakata, Sakurai, Yokoyama, et al., 1997); unemployment (Arnetz, Brenner, Levi, Hjelm. Petterson, Wasserman, et al., 1991); and the aftermath of natural disasters such as hurricanes and earthquakes (Ironson, Wynings, Schneiderman, Baum, Rodriguez, Greenwood, et al., 1997; Solomon, Segerstrom, Grohr, Kemeny, & Fahey, 1997). Worthy of note, Ironson and colleagues (1997) found that intrusive ruminations that occurred over a prolonged period among victims of a hurricane were associated with lower levels of natural killer (NK) cells. Researchers have found intrusive thoughts may actually maintain stress-related immune changes and higher subjective levels of distress (La Via, Munno, Lydiard, Workman, Hubbard, Michel, & Pauling, 1996). There is also a relationship between prolonged intrusive ruminations and maladaptive psychological functioning, possibly providing one mechanism for ongoing immune dysregulation (Baum, Cohen, & Hall, 1993). The best predictors of developing colds were stressors that lasted one month or more (Cohen, Frank, Doyle, Skoner, Rabin, & Gwaltney, 1998) in volunteers that had been inoculated with several different strains of cold viruses.

Alzheimer's disease and related disorders (ADRD) and long term spousal care

The stress of providing long-term care for a parent or spouse with ADRD has been associated with prolonged immune and endocrine dysregulation, in addition to health changes such as alterations in wound healing, vaccine response, elevated blood pressure, and depressive symptomatology (Castle, Wilkens, Heck, Tanzy & Fahey, 1995; Grant, Adler, Patterson, Dimsdale, Ziegler, & Irwin, 2002; Irwin, Brown, Patterson, Hauger, Mascovich, & Grant, 1991; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Malarkey, Wu, Cacioppo, Malarkey, Poehlmann, Glaser, et al., 1996; McGuire, Kiecolt-Glaser, & Glaser, 2002; Mills, Yu, Ziegler, Patterson, & Grant, 1999; Vedhara, Cox, Wilcock, Perks, Hunt, Anderson, et al., 1999; Vitaliano, Scanlan, Ochs, Syrjala, Siegler, & Snyder, 1998). After caregiving ends, these changes may persist (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994; Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998).

Immune function and ADRD caregiving

The first study to examine immune function in the context of ADRD caregiving was conducted by Kiecolt-Glaser, Glaser, Dyer, Shuttleworth, Ogrocki, & Speicher, (1987). Participants were caregivers (N= 34, mean age 60) and matched noncaregivers (N=34, mean age 60). Significant differences were found between the caregivers and noncaregivers ($p \leq .05$), with caregivers having lower percentages of total T lymphocytes and helper T lymphocytes, as well as a significantly lower CD4+/CD8+ ratio. Additionally, caregivers had significantly higher ($p < .05$) antibody titers to latent

Epstein-Barr virus (EBV) than did controls. The overall conclusion was that caregivers had poorer cellular function than noncaregivers.

In a contrasting result, Reese, Gross, Smalley, & Messer (1994) compared three groups of equal size (N=25): AD caregivers (mean age 56), stroke caregivers (mean age 64), and noncaregivers (mean age 61). While AD caregivers reported more distress than the other groups, no significant differences were found among groups on a battery of quantitative immunological assays. As mentioned in Chapter 1, functional rather than quantitative assays are more likely to find more consistent stress-related differences in immune function. Additionally, there was a significant difference in age between the younger AD caregivers and the other groups, which would typically have suggested a slightly better functioning immune system.

In a controlled longitudinal study investigating change in the pro-inflammatory cytokine Interleukin-6 (IL-6) over the course of six years in a spousal dementia caregiver population, the researchers (Kiecolt-Glaser, Preacher, MacCallum, Atkinson, Malarkey, et al., 2003) hypothesized that the caregivers would show a steeper increase in IL-6 levels over time than noncaregiving controls. They recruited 225 participants (65 male, 160 female). Of those, 119 were spousal dementia caregivers, and 116 were controls. Subjects with immunologically related health problems (cancer, recent surgeries) or taking medications with immunological consequences were excluded from the study. Age on study entry ranged from 55-89 (Mean = 70.58, SD =8.03). There were no significant differences between the cohorts on proportion of females, age, ethnicity, or education. Interestingly, education was used as a substitute for socioeconomic status, as many of the caregivers were older females who had never worked outside the home. The one area

where the cohorts did differ significantly at entry ($p < 0.001$) was marital status, with the control group having fewer intact marriages. However, with lower rates of morbidity and mortality as well as better immune function being associated with intact marriages (House, Landis, & Umberson, 1988), this actually worked against confirmation of the experimental hypothesis. Results indicated that the rate of increase in levels of IL-6 was about 400% greater for caregivers than for non-caregivers ($p = 0.02$). Neither gender nor ethnicity ($p = 0.176$) were significant predictors of change in IL-6 levels during the course of the study.

Additionally, the question of bereavement was addressed, as 50 of the 119 spouses involved died during the 6-year course of the study. Interestingly, there were no statistically significant differences between current and former caregivers in change in IL-6 levels ($p = 0.571$), or absolute IL-6 levels ($p = 0.34$) during the course of the study. Thus, even several years after the death of a spouse, the mean rate of increase in IL-6 among the bereaved caregivers did not differ from that of the current caregivers (Kiecolt-Glaser, Preacher, et al., 2003).

Another study (Lutgendorf, Garand, Buckwalter, Reimer, Hong, & Lubaroff, 1999) compared IL-6 levels in female Alzheimer caregivers ($N = 18$, mean age 70.9) to older women assessed 1 month before moving their primary residence ($N = 17$, mean age 79.6); nonmoving and noncaregiving older women ($N = 15$, mean age 76.1); and younger women ($N = 20$, mean age 39.9). Results indicated that there was a significant difference among groups ($p < .001$), with mean IL-6 levels ordered as expected across groups: AD caregivers ($5.70 \text{ pg/ml} \pm 4.30$); movers ($3.32 \text{ pg/ml} \pm 3.12$); older controls ($2.44 \text{ pg/ml} \pm$

1.60); younger controls ($1.11 \text{ pg/ml} \pm .76$). Caregivers had significantly ($p < .005$) higher IL-6 levels than older controls; than movers ($p < .03$); and younger controls ($p < .001$).

On entry into a longitudinal study conducted by Keicolt-Glaser, Dura, Speicher, Trask, and Glaser (1991), and again at the 13 month mark, spousal caregivers of dementia patients ($N = 69$, mean age 67) reporting lower levels of social support, and those who were the most distressed by dementia-related behaviors showed the largest and most consistently negative changes in immune system functioning compared to matched controls ($N = 69$). Three immune measures were utilized: antibody titers to latent EBV and lymphocyte proliferation to Con A and PHA. Caregivers showed increased antibody titers over time compared to controls, and decreased proliferative response to both Con A and PHA over time compared to controls. Interestingly, the groups did not differ significantly on quantitative measures of immune function.

Additionally, researchers have found significant differences between spousal caregivers and controls on measures of delayed hypersensitivity skin testing (McCann, 1991), with spousal caregivers showing poor immune function relative to a comparison sample, and to age-based norms as well; Plasma levels of neuropeptide Y (NPY), which are negatively correlated with NK cell activity, were significantly elevated in older spousal caregivers compared to levels found in older controls (Irwin, Brown, Patterson, Hauger, Mascovich, & Grant, 1991). In another study measuring NK cell activity, spousal caregivers reporting lower levels of social support, as well as less closeness in their important interpersonal relationships, demonstrated poorer augmentation of NK cell activity in response to two cytokines compared to caregivers who showed a greater degree of NK augmentation (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994).

A recent study (Gallagher-Thompson, Robinson-Shurgot, Rider, Gray, McKibben, Kraemer, et al., 2006) using salivary cortisol as a dependent variable showed support for a relationship between chronic stress and HPA dysregulation. Participants were women (N=83) divided into familial dementia caregivers (n = 44) or non-caregivers (n = 39). Groups consisted of both Hispanic (20 caregivers; 19 noncaregivers) and Non-Hispanic White (NHW; 24 caregivers, 20 noncaregivers) participants. Groups were matched for age and education (Hispanic CG=11, NCG=6; NHW CG=14, NHW NCG=14). Results showed that caregivers had greater cortisol levels throughout the day compared to noncaregivers, regardless of ethnicity. However, cortisol slopes did differ between the ethnicities, regardless of caregiver status. This study also used the CES-D, and did not find a relationship between symptoms of depression and morning levels of salivary cortisol.

Psychological Modifiers of Immune Dysregulation

Immunological dysregulation has been associated with negative affect in a number of studies examining temporary, experimentally induced mood changes to chronic stress and clinical depression (Kiecolt-Glaser, Malarkey, Cacioppo, & Glaser, 1992; Herbert & Cohen, 1993). Negative affect has also been associated with a decrease in antibody response to an orally ingested antigen, varying on a daily basis according to diary reports of positive and negative moods (Stone, Neale, Cox, Napoli, Valdimarsdottir, & Kennedy-Moore, 1994). Fluctuations in negative mood over the course of a day were associated with reduced NK cell lysis among female subjects, with positive mood moderating that association (Valdimarsdottir & Bovbjerg, 1997). In healthy older adults, the association

between reduced NK cell lysis and the stressor of moving was partially mediated by decreased positive mood (Lutgendorf, Vitaliano, Tripp-Reimer, Harvey, & Lubaroff, 1999).

Changes in NK activity in response to stress have been shown to be associated with diversity in cortical activation, with decreases in NK activity occurring in individuals with greater right pre-frontal activation as compared to individuals with greater left pre-frontal cortical activation (Davidson, Coe, Dolski, & Donzella, 1999). These data supply additional supporting evidence for the association of left pre-frontal activation with positive emotions, and greater right pre-frontal cortex activation being associated with the expression and experience of negative emotion (Davidson, Jackson, & Kalin, 2000).

One conceptualization has been that negative affect functions as a critical pathway for other psychological modifiers such as personal relationships and personality (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). One of the most robust findings in the PNI literature is the link between personal relationships and immune function (Uchino, Kiecolt-Glaser, & Cacioppo, 1996). Specifically: higher social support in spouses of men being treated for urological cancer resulted in higher NK cell activity compared to those women with less social support (Baron, Cutrona, Hicklen, Russell, & Lubaroff, 1990); a stronger immune response to a Hep B vaccine was displayed by medical students who reported good social support compared to those who reported less support (Glaser, Kiecolt-Glaser, Malarkey, Kennedy, & Hughes, 1992); and greater susceptibility to respiratory viruses was reported by individuals with fewer social ties (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997).

In support of the stress moderating effect of social support, a 1997 study by Koenig, Cohen, George, Hays, Larson, and Blazer examined the relationship between religious attendance and IL-6 levels over 6 years. Subjects (N = 1718, age > 65) were given three interviews (baseline and three years apart), and had blood drawn for immune analysis. When analyzed as a dichotomous variable, results indicated a significant ($p < .01$) inverse relationship between religious attendance and IL-6 levels.

Discordant close relationships

Discordant close relationships have been associated with immune dysregulation (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Numerous studies have shown marital conflict and associated hostile behaviors in newlyweds, as well as couples married an average of 42 years, to be associated with pervasive differences in endocrine and immune system function (Kiecolt-Glaser, Glaser, Cacioppo, MacCallum, Snydersmith, Kim, et al., 1997; Kiecolt-Glaser, Glaser, Cacioppo, & Malarkey, 1998; Kiecolt-Glaser, Bane, Glaser, & Malarkey, 2003). The above cited studies support the conclusions that immune functioning is better in close supportive personal relationships, and that persistent immune dysregulation may be provoked by chronically stressful or abrasive close personal relationships (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

Personality and coping styles

Building on the findings for social support and negative affect, personality or coping styles associated with negative social relationships or moods might have consequences in immune dysregulation. Segerstrom (2000) found dysregulation of immune function on a cellular level as well as altered leukocyte counts in peripheral blood associated with personality and coping styles such as attributional style, repression, rejection sensitivity,

and sociability. In contrast, the associations of optimism with coping ability, more positive moods, and differences in responses to stress have been linked to mediation of better immune function among law students in their first year of study (Segerstrom, Taylor, Kemeny, & Fahey, 1998). Situational optimism regarding health outcomes was shown to be related to slower immune system decline, delayed symptom onset, and an extended survival time in a sample of HIV-infected males (Kemeny, 1994; Reed, Kemeny, Taylor, & Visscher, 1999). In a healthy older adult population, the association between anticipation of moving and reduced NK cell lysis was moderated by a sense of coherence, which is viewed as an indicator of dispositional resilience; the poorest level of NK cell lysis was associated with a low sense of coherence (Lutgendorf, Vitaliano, Tripp-Reimer, Harvey, & Lubaroff, 1999).

Differences in appraisals of an event, as well as reactions to that same event, can provoke different endocrine and immune responses (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Additionally, the associations between personality, coping styles and immune function may be mediated by neuroendocrine mechanisms (Segerstrom, 2000).

Coping and ADRD Caregivers

Lazarus and Folkman (1980) defined coping styles in their transactional model of coping and stress as the behavioral and cognitive efforts to manage internal and external demands that are appraised as depleting or exceeding one's resources. An individual's coping style may be influenced by situational and dispositional factors. Successful coping may be distinguished from unsuccessful coping by the use of active versus avoidant coping methods. Active coping may be applied cognitively, resulting in a positive

reappraisal of the situation, or behaviorally, resulting in an action that reduces or eliminates the stressor. Active coping has been conceptualized as including two domains of coping: problem-focused, which includes efforts directed at changing the person-environment relationship; and emotion-focused, which includes efforts attempting regulation of the emotional response to the situation (Kneebone & Martin, 2003; Stowell, Keicolt-Glaser, & Glaser, 2001; Vitaliano, Russo, Carr, Maiuro, & Becker, 1985). While problem-focused coping has been associated with less depression, physical symptoms, and improved quality of life (Kneebone & Martin, 2003), in chronic stress situations both problem- and emotion-focused coping may have positive effects on overall well-being and health (Stowell, et al., 2001). The participants in this study were familial ADRD caregivers, and caregiving for a family member suffering from ADRD has been conceptualized as a model of chronic stress (Dura, et al., 1991; Schulz, et al., 1995; Keicolt-Glaser, et al., 1991; Schulz, et al., 1990; Wisnewski, et al., 2003).

In a cross-sectional study that examined whether coping methods were related to immune function and stress level (Stowell, et al., 2001), the researchers assessed perceived stress and coping method (active or avoidance coping) in healthy older adults (N = 173, mean age 62.4 years). Participants were either current familial caregivers of dementia patients (n = 61), former familial caregivers of dementia patients (n = 34), or in the non-caregiver comparison group (n = 78). The study hypothesized that active coping would moderate the effects of chronic stress on both physical and mental health, while avoidance coping would magnify those effects. Immune function was measured quantitatively with number and percentage of CD3+, CD4+, and CD8+ T lymphocytes and functionally with proliferative response of peripheral blood leukocytes to PHA and

Con A. Results suggested both active and avoidant coping were significantly related to an increased proliferative response to PHA and Con A. However, higher levels of active coping were significantly related to the proliferative response at high stress levels, while avoidant coping was significantly related to the proliferative response at low stress levels. Stowell and colleagues suggested that the results indicated support for the idea that perceived stress level affects the relationships between coping methods and immune function.

In an article especially on-point for the current research, Kneebone and Martin (2003) reviewed sixteen studies (12 cross-sectional and 4 longitudinal) that were based on Lazarus and Folkman's (1984) coping model and that focused on the coping of caregivers of persons with dementia. The review aimed to examine the clinical applicability of the research on dementia caregiver coping to interventions attempting to improve caregiver adjustment. In the studies reviewed, caregivers were spouses, sons, daughters, and significant others all of whom were providing care for noninstitutionalized dementia patients in the community. Measures of coping used in the studies reviewed varied, ranging from researcher specified diagnostic criteria, to indexes of life satisfaction, to measures of variables specific to caregivers, labeled as 'caregiver burden' (Kneebone & Martin, 2003). The authors overall conclusion was that a general tendency towards acceptance and problem-solving styles of caregiving is probably advantageous to caregivers of AD/RD patients. However, the ability of the research to inform clinical practice is limited due to methodological flaws and differences in theoretical perspective.

Two measures specifically based on Lazarus and Folkman's (1984) stress and coping model were employed in three of the studies reviewed: the Ways of Coping Checklist

(WCCL; Aldwin, Folkman, Shaefer, Coyne, & Lazarus, 1980), and the Ways of Coping Checklist-Revised (WCCL-R; Vitaliano, Russo, Carr, Young, Maiuro, & Becker, 1985). Neundorfer (1991) used the WCCL (Aldwin, et al., 1980) in a cross-sectional design with spousal caregivers (N = 60) of ADRD patients. He found significant positive correlations between reduced physical health, increased depression and anxiety, and emotion-focused coping. Neundorfer described emotion-focused coping as “escape and avoidance” (wishing the situation would go away), “confrontive coping” (angrily confronting the ADRD patient) and “accepting responsibility” (blaming and criticizing self for the problems). Vitaliano, Russo, Young, Teri, and Maiuro (1991) conducted a longitudinal study that assessed spousal caregivers of ADRD patients at time 1 (N = 95) and time 2 (N = 79), which was 15-18 months later. Using the WCCL-R they found a significant relationship between initial and later caregiver burden on only one dimension of coping, that of ‘Counting one’s blessings’ (i.e., compared myself to others who were less fortunate). This strategy correlated negatively with baseline and follow-up burden. Interestingly, this dimension of coping seems to be more emotion focused (using a strategy that seems to regulate feelings) and generated findings contrasting to those of Neundorfer (1991) but supporting the results of Stowell et al. (2001). In another study using the WCCL-R (McKee, Whittick, Ballinger, Gillhooly, Gordon, Mutch, et al., 1997), the researchers employed a cross-sectional design comparing family supporters of older adults who had a diagnosis of dementia (n = 114) to family supporters of older adults who did not have a diagnosis of dementia (n= 114). Results indicated that regardless of dementia diagnosis, family supporters who reported using a problem-focused strategy scored higher on measures of self-perceived coping.

The Coping Response Inventory (CRI; Moos, 1988) was used in two studies (Goode, Haley, Roth, & Ford, 1998; Haley, Roth, Coleton, Ford, West, & Collins, 1996). Haley and colleagues (1996) compared black (n = 123) with white (n = 74) dementia caregivers and found an overall better adjustment of black versus white caregivers. They speculated that difference in adjustment was not due to the effects of race per se, but rather the result of differential use of coping strategies between the groups. In the combined sample (N = 197), avoidance coping was found to be positively associated with depression and negatively associated with a life satisfaction measure. Approach (active) coping was found to be negatively associated with depression and positively associated with the life satisfaction measure. Goode et al. (1998) also used a longitudinal design, with the original caregiver participants (N = 197) being re-assessed at 12 months (n = 122). They found that use of “approach (active) coping was associated with decreased depression and fewer changes in physical health as compared to use of “avoidance coping”.

Two other studies (Pett, Caserta, Hutton, & Lund, 1988; Wright, 1994) employed the Jaloweic Coping Scale (JCS; Jaloweic, Murphy, & Powers, 1984). Pett and colleagues (1994) had findings similar to that of Neundorfer (1991) in a sample (N = 181) of female middle-aged caregivers. Results indicated that caregivers identified as being “at risk” (i.e., high burden and low life satisfaction) were more likely than caregivers classified as “low risk” to use avoidant and evasive coping. In the Wright (1994) study, the author used a longitudinal design with a control group. Spousal caregivers of AD/DRD patients (N = 30) were compared to 17 healthy couples (N = 34) to measure coping at baseline and at a 2-year follow-up. Due to change in status, coping was considered in three

different categories: spouses continuing with in-home caregiving ($n = 12$), widowed spouses ($n = 8$), and nursing home placement spouses ($n = 7$). For continued in-home caregivers, baseline coping strategies were unrelated to health outcomes at follow-up. For widowed spouses, high use of “palliative coping (cognitive and stress reduction strategies) at baseline was associated with higher levels of depressed mood at baseline as well as follow-up and poorer health at follow-up. For caregivers who had placed their spouses in nursing homes, “confrontive coping” (i.e., actively trying to change the situation) was associated with fewer depressed moods at follow-up. The differences in results for the three groups of caregivers support the view that coping strategies may be differentially effective depending on caregiving context and circumstances (Stowell, et al., 2001; Vitaliano, et al., 1985) and therefore support the predictions of the Lazarus and Folkman model (1984).

Two other studies (Gallagher, Wagenfield, Baro, & Haepers, 1994; Saad, Hartman, Ballard, Kurian, Graham, & Wilcock, 1995) used the Caregiver Coping Measure (CCM; Pearlin, Mullan, Semple, & Skaff, 1990). The CCM was devised specifically for caregivers. It measures coping along three dimensions: management of meaning (MM; e.g., ‘try to keep a sense of humor’); management of the situation (MS; e.g., ‘try to find ways to keep your relative busy’); and management of the symptoms of distress (MSD; e.g., ‘drink some alcohol’). In the Gallagher et al. (1994) study, “role overload” was investigated among caregivers, consisting of dementia caregivers ($n = 55$) and caregivers to older adults with other chronic conditions ($n = 71$). Results indicated that MM was negatively related to role overload in dementia caregivers. For both caregiver groups,

within MS, 'let things slide' was related to greater role overload, as was 'take medication' in MSD.

Saad and colleagues (1995) used depression as a measure of adaptation in dementia caregivers (N = 109). They found that scores on MS related to increased likelihood of depression, whereas those caregivers using the MM strategy were less likely to be depressed.

Pratt, Schmall, Wright, & Cleland, (1985) used the Family Crisis Oriented Personal Evaluation Scales (F-COPES; McCubbin, Larsen, & Olsen, 1981) in their study with caregivers (N = 240) to ADRD patients. Pratt and colleagues found significant negative correlations between caregiver burden and 'confidence in problem solving', 're-framing problems', 'seeking spiritual support, and 'seeking family support'. 'Passivity' was positively associated with caregiver burden. Hinrichsen & Niderehe (1994) found that avoidance coping was significantly related to increased burden, and active cognitive coping with decreased burden in familial ADRD caregivers (N = 152). Pruchno & Resch (1989) found that 'wishfulness' (avoidant coping) was associated with poorer adjustment in spouse caregivers (N = 315) to ADRD patients.

Lastly, two studies (Almberg, Grafstrom, & Winblad, 1997; Gottlieb & Cignac, 1996) used coded question responses and interview transcript content analyses in their research. Almberg et al. divided familial caregivers (N = 46) of ADRD patients into two groups, comparing those who reported burnout (n = 17) with those who were non-burnout (n = 29). They found that the burnout group reported higher use of emotion-based coping than the non-burnout group, and that the non-burnout group reported a higher use of more problem-based coping than the burnout group.

Gottlieb and Cignac (1996) interviewed familial ADRD caregivers (N = 51). They asked participants to describing coping in regards to two stressor domains: (1) 'the most upsetting behavioral or cognitive symptom of disease' ("symptom"), and (2) 'a deprivation occasioned by the caregiving role' ("deprivation"). Content analysis of interview transcripts established 53 categories of coping within 11 classes. Five classes were considered important, with all coping being assessed specifically to the experience of the caregivers. Caregiver adjustment was determined by measures of life satisfaction, psychiatric symptoms and perceived physical health. Analysis was conducted within stressor domains: results for the deprivation domain indicated that 'making meaning' and 'positive framing' were significantly related to better health. In the symptom domain, 'positive framing' was related to poorer physical health, 'verbal management' with less life satisfaction and increased psychiatric symptoms, and 'emotional inhibition' (i.e., 'admonishes self not to express emotion') significantly correlated with life satisfaction.

In conclusion, overall findings offer support to Kneebone & Martin's (2003) conclusion that a general tendency towards acceptance and problem-solving styles of caregiving (i.e., active strategies) is probably advantageous to caregivers of ADRD patients while emotion-focused strategies have a higher likelihood of leading to adjustment difficulties. While results are mixed, the research indicates support for the view that coping strategies may be differentially effective, depending on caregiving context and circumstances (Stowell, et al., 2001; Vitaliano, et al., 1985), and support the predictions of the Lazarus and Folkman model (1984). Ultimately, however, the ability of the research to inform clinical practice is limited due to methodological flaws and differences in theoretical perspective.

Hardiness

Brief Introduction

In contrast to the transactional model of coping and stress advanced by Lazarus and Folkman (1980), hardiness was conceived of as a personality disposition. It was originally formulated as a set of attitudes motivating an individual to respond to stressful circumstances in an adaptive manner (Kobasa, 1979); as a buffer between stress and illness; and “an inherent health-promoting factor in a stress-laden human environment” (Bigbee, 1985, p. 55; as quoted in Dibartolo & Soeken, 2003).

The study of hardiness began in 1975 with a 12-year, longitudinal study of stress reactions in male and female managers at Illinois Bell Telephone (IBT). Each year the managers completed a battery of psychological and medical tests. In 1981, at the midpoint of the study, AT & T, the parent company of IBT, was forced to divest itself of its subsidiaries in the federally ordered de-regulation. As a result, IBT went from 26,000 employees in 1981 to 14,000 in 1982 (Maddi & Kobasa, 1984). Two-thirds of the study sample showed evident signs of being impacted by extreme stress such as suicides, violence in the workplace, heart attacks, strokes, cancer, depressive and anxiety disorders. However, the remaining one-third actually thrived, experiencing success at work (whether with a new employer or IBT), in relationships, and generally feeling enlivened (Maddi, 2004). The effort to qualify the difference between the two groups led to the discovery of hardiness.

The personality disposition of hardiness was originally formulated as a set of attitudes motivating an individual to respond to stressful circumstances in an adaptive manner. Sometimes conceptualized as existential courage, it is that elusive quality that

enables one to tolerate the anxiety of uncertainty (Maddi, 2004), and provides the motivation to actively change disaster into opportunity (Kobasa, 1979; Maddi & Kobasa, 1982; Maddi, 2004). Specifically, the attitudes and beliefs that constitute hardiness are commitment, control, and challenge (the 3 C's). Individuals strong in commitment look to involvement with others to find experience and meaning, and avoid the waste of alienation and isolation. Strength in control leads to a desire and willingness to struggle to have an influence on the outcomes going on around one. Lastly, strength in challenge is finding the struggle to learn and grow from any experience "developmentally fulfilling" (Maddi, 2004). The quality of hardiness is believed to "buffer" the effects of stress on illness (Kobasa, 1979; Maddi, 1990; Maddi & Khoshaba, 1994, 1999; Maddi & Kobasa, 1984), and is related to Lazarus and Folkman's (1984) model of stress, appraisal, and coping (Maddi, 1990). Additional research has shown a positive relationship between hardiness and such diverse areas as performance in basketball players (Maddi & Hess, 1992); military applications, such as success rates in officer training school (Florian, Milkulincer & Taubman, 1995; Westman, 1990) and effective leadership behavior among West Point cadets (Bartone & Snook, 1999); and retention rate among at-risk community college students (Lifton, Seay & Bushke, 2000).

The construct validity of hardiness has been elaborated in an experiential sampling study (Maddi, 1999); participants were paged randomly and asked to comment on the nature of their activities at that time. Results indicated that there was a positive relationship between hardiness and involvement with others and events (seen as commitment), the sense that their activities had been chosen and thus could be influenced (seen as control), and that there was a positive process of learning from what was going

on (viewed as challenge). Maddi (1986, 1994, 1997, 2002) has hypothesized hardiness as a provider of the courage and motivation to implement beneficial health behaviors, such as coping, self-care, and social support seeking.

The measure of hardiness: Personal Views Survey

The first measure of hardiness was devised on working adults (Kobasa, Maddi, & Kahn, 1982) and used six scales from other instruments that seemed to measure commitment, control, and challenge. This questionnaire led to the early criticisms that hardiness was not a unitary characteristic, with challenge being unrelated to commitment and control in some samples, and simply the opposite of negative affectivity, or neuroticism (Funk & Houston, 1987; Hull, Van Treuren & Virnelli, 1987).

In terms of the question of the non-unitary quality of hardiness, one of the scales used to measure challenge emerged as the major difficulty. College students interpreted the items on this scale differently than working adults, leading to a unitary measure in the latter population, and a non-unitary measure in the former population (Maddi, 1997). On the question of redundancy of hardiness with negative affectivity, the problem appeared to be that several of the scales initially used to measure the former characteristic included only negatively worded items (Maddi, 1997).

The Personal Views Survey-II (PVS II; Maddi, 1997) was designed to correct methodological criticisms of earlier iterations by balancing positive with negative indicator items, demonstrably measuring a different concept than negative affectivity or neuroticism, and having a more homogeneous item format (Wiebe & Williams, 1992; Maddi, et al., 1996). In an experiential sampling study based on Csikszentmihalyis (1975), participants (N = 20) who had taken the PVS-II one month earlier were paged 10

times per day for 1 week. At the time of each beep participants filled out a short questionnaire detailing the nature of their activities and experience. Results supported the construct validity of hardiness by demonstrating that high scorers on the PVS-II had a consistent experience of commitment, control, and challenge in their moment-to-moment activities (Maddi, 1999). The resulting instrument was a 50-item rating scale and is a third-generation measure of hardiness with adequate reliability. Internal consistency scores range from .70-.75 for commitment, .61-.84 for control, and .80-.88 for challenge (Maddi, 1997), with a coefficient alpha of .84 for the total Hardiness score (Maddi, Khoshaba, Persico, Lu, Harvey, & Bleeker, 2002) and 6-month stability estimates around .60. (Maddi, Wadhwa, & Haier, 1996). The PVS-III-R used in the present study is derived from the 18 best items from the PVS-III, which in turn consists of the 30 best items of the PVS-II.

Hardiness and caregivers

This section briefly reviews the studies assessing hardiness in caregivers. A search using *Digital Dissertations*, *Medline*, *Psyclit* and *Psycinfo* employing the key words hardiness, intervention, and caregivers yielded a total of fifteen studies. Of those studies, eleven were unpublished dissertations. Overall, study results were mixed, which may be attributable to the variety of measures, lack of controlled comparisons, unreported psychometric properties, and several small sample sizes. However, hardiness did consistently emerge as a measurable factor affecting physical and mental health (see Table 1).

A variety of measures were used in the studies reviewed, with 12 of the studies using some version of a standardized measure of hardiness, such as the Health Related

Hardiness Scale (HRHS; Pollock & Duffy, 1990; 3 studies), the Family Hardiness Index (FHI; McCubbin, McCubbin, & Thompson, 1991; 4 studies), or a version of the Personal Views Survey (Maddi, 1990, 5 studies). The remainder of the studies (3 studies) used some form of interview alone or in conjunction with standardized or non-standardized instruments.

All the studies using an iteration of the PVS (Jensen, 1996; Johnson, 1994; Nunley, 2002; Sussman, 2003) in this section are unpublished dissertations. Jensen (1996) focused on examining the interaction between various factors in the caregivers environment and the potential mediating role of coping mechanisms on caregiving appraisal, using the theoretical framework of Roy's Adaptation model of nursing (which posits an intermediary role of coping mechanisms on caregiving role appraisal) and the Lazarus and Folkman (1984) theory of stress and coping. Caregivers (N = 129) were either wives or daughters of an ADRD sufferer living at home. Using structural equation modeling (SEM), a significant relationship between caregiver physical health, ADRD patient problem behaviors, emotion and problem-focused coping, and appraisal of the caregiving role was demonstrated. An indirect relationship between hardiness, depression, social support, spirituality, and caregiving role appraisal was present through problem and emotion-focused coping. The author concluded that results provided support for the Roy Adaptation model and initial confirmation that caregiving role appraisal can include positive aspects for the caregivers.

Johnson (1994) studied familial caregivers (N = 60) of chronically ill children. She examined the relationship of hardiness, financial burden, demands of childcare, personal strain, social support, familial/social impact, and demographic variables to

depression, anxiety, and somatization in the caregivers, using a descriptive correlational design. Results indicated that 90% of caregivers considered the demands of child care to be minimally difficult, but only 73.4% believed that the family was coping well overall. Few caregivers noted anxiety, depression, and somatization, and the mean for hardiness scores indicated that the majority of caregivers were in the moderate to high hardy range. It was concluded that for this caregiver group, social support and hardiness are very important for stress reduction.

Nunley (2002) used spousal caregivers who were over the age of 60 ($N = 44$) and caring for an ADRD patient, hypothesizing that hardiness would buffer the effects of ADRD patient problem behaviors on caregiver distress. Using multiple regression, support was found for the hypothesized buffering effect of caregiver hardiness on the strain arising from care-recipient problem behaviors. Perception of caregiver burden and quality of life were found to be modified by the hardiness of the caregiver as well. Using the CES-D, Nunley also found that hardy caregivers experienced fewer depressive symptoms irrespective of the level of ADRD patient behavioral problems. In the last dissertation to utilize the PVS, Sussman (2003) assessed caregivers ($N = 42$) of institutionalized ADRD patients. Results indicated that caregiver hardiness was positively associated with support-seeking and problem-focused coping strategies and predictive of lower levels of depression, and that caregiver hardiness and problem-focused coping strategies were both predictive of lower levels of anxiety symptoms. Additionally, there was a negative relationship found between caregiver hardiness, avoidant coping and wishful thinking.

Overall, findings supported the relationship between caregiver hardiness and preference for adaptive coping strategies. These strategies, in turn, are correlated with decreased levels of emotional distress. One study (Johns, 1998), also an unpublished dissertation, used an early version of the PVS known as the Hardiness Test (HT, Hardiness Institute, 1988). Participants were informal caregivers (N = 30) of HIV+/AIDS patients, and the author examined the relationship between personality hardiness and burnout in these caregivers. Results revealed a significant negative relationship between burnout and hardiness scores.

Four studies (Clark, 2002; Henkle, 1994; Stevens, 1997; Uthis, 2000) used the Family Hardiness Index (FHI; McCubbin, McCubbin, & Thompson, 1991). In one of the four articles published in peer-reviewed journals, Clark studied female familial caregivers (daughters, N = 67, mean age 55) examining the effects of individual and family hardiness, transformational coping, and help-seeking on caregiver stress levels. Care recipients were adults ≥ 50 (mean age 75.3) with primary health problems of Alzheimer's disease, hypertension, and/or cerebral vascular disease. Using a nonexperimental, cross-sectional design, Clark (2002) found that hardiness was significantly related to fatigue and depression. Family hardiness and Individual hardiness were significantly related, with family hardiness being related to the overall effectiveness of the caregiver and transformational coping; individual hardiness was negatively related to depression and fatigue, and positively related to transformational coping. Clark's results seem to support the influence of the family on the individual member and argue for the importance of assessing the caregiver's family in the course of intervention exploration.

Table 1. Hardiness and caregivers.

Authors	N	Measures	Study Components	Findings
Clark, L. 1996	53; familial caregivers (CGs)	Interview	Correlation between hardiness and CG distress and physical health	Neg. relationship (R/T) between hardiness and psychological distress; no R/T between hardiness & physical health
Clark, P. 2002	67; CGs of disabled adults (DA)	Dispositional Resiliency Scale (DRS); Family Hardiness Index (FHI); Center for Epidemiological Studies-Depression (CES-D); Piper Fatigue Scale (PFS); Help-Seeking Scale (HSS)	Descriptive, cross-sectional design; convenience sample; examined effects of individual & family hardiness on CG depression & fatigue	Fatigue & depression sig. related; individual & family hardiness sig. related; individual hardiness neg. related to dep. & fatigue, pos. related to transformational coping. Family hardiness pos. related to trans. coping use, & help seeking.
DiBartolo et al., 2003	72; spouse CGs of ADRD pts.	Health Related Hardiness Scale (HRHS)	Convenience sample; mailed survey; addressed R/T between hardiness, coping, appraisal, self-appraised health.	Hardiness moderated appraisal of caregiving challenges.
Henkle, 1994	110 CG/care recipient (CR) dyads. Family CGs of functionally impaired, cognitively intact older adults.	FHI, Caregiver Burden Scale (CBS), Family Crisis oriented Personal Scale (F-COPES), Medical Outcome Scale (MOS), Life-3 scale.	Descriptive, non-experimental, correlational study. Explored R/T among demographics, family hardiness, burden, appraisal, coping, and well being.	CGs who described high personal benefit from caregiving had sig. Higher FHI scores, felt less stress and threat. FH found to be important resource for stress and burden of familial caregiving.

Table 1. Hardiness and caregivers (cont.)

Authors	N	Measures	Study Components	Findings
Jensen, 1996	129; wives or daughter CGs of ADRD pts. at home	CES-D; Personal Views Survey (PVS); Global Self-Rated Health Scale (GHS); Lubben Social Network Scale (LSNS); Memory and Behavior Checklist (MBCL); Ways of Coping Revised (WOCR); Caregiver Appraisal tool.	Quasi-experimental design based on Lazarus and Folkman (1980) and Roy Adaptation model of nursing; examine R/T of factors in CGs environment and coping behaviors on caregiving appraisal	Hardiness indirectly related to appraisal through problem and emotion based coping
Johns, 1998	30; informal CGs of HIV pts.	Burnout Measure; Hardiness Test (HT)	Examine R/T between hardiness and burnout	Sig. neg. R/T between hardiness & burnout
Johnson, 1994	60; Family CGs of chronically ill children	Child Care Experience Scale (CCES); impact on Family Scale (IFS); Perceived Social Support Index (PSSI); PVS; SCL-90-R.	Descriptive correlational design. Investigated R/T between several caregiving stressors, hardiness, and anxiety, depression, and somatization in this CG group.	Hardiness and social support together were sig. neg. correlated with child care demands, personal strain, stress, and familial/social impact. Concluded social support and hardiness important for stress reduction in this CG group.
Kulik, 2001	259; elderly Israeli female spousal CGs	Interview	Examined three aspects of spousal caregiving: commitment; perceived harmful effects; delegating responsibility to others.	Women with high levels of emotional hardiness less likely to delegate responsibility for caregiving.

Table 1. Hardiness and caregivers (cont.)

Authors	N	Measures	Study Components	Findings
Matthews, 1995	12; ADRD spousal CGs	Open and semi-structured interviews.	Explore source and frequency of CG information used to assist CGs in the CG role.	Hardiness, social support, and reflective practice viewed as important components in learning the CG role.
McKinney, 2000	31; family CGs of cancer pts.	HRHS, CES-D, Exercise of Self-care Agency, Threat Scale.	Predictors of anxiety, depression and perceived health identified using Lazarus stress theory.	Less hardy CGs at risk for self-care disturbances. Support found for Lazarus stress and coping theory.
Nunley, 2002	44; elderly spousal caregivers of ADRD pts.	Personal Views Survey-III (PVS-III); Caregiver Burden Inventory (CBI); Behavioral Problem Checklist (BPCL); CES-D.	Volunteer sample; examined hardiness as buffer of distress	Hardy CGs experienced fewer depressive symptoms; hardiness buffers effect of behavioral problems on CG burden.
O'Brien, 1994	59; familial CGs of frail elders	HRHS, Mental Health Index, Caregiver Strain Index.	Self-selected sample; examined R/T among hardiness, burden, psychological well-being and several CG characteristics.	Hardiness neg. R/T burden; hardiness scores higher in African-Americans and females.
Stevens, 1997	80; 40 pt-CG dyads; elderly stroke pts. & primary CGs	FHI; General Self-Efficacy Scale (GSES); BAI; Geriatric Depression Scale (GDS)	Examine R/T between coping skills and affective responses	Sig. R/T found between coping skills and affective responses for both CGs and pts.

Table 1. Hardiness and caregivers (cont.)

Authors	N	Measures	Study Components	Findings
Sussman, 2003	42; CG of ADRD pts.	PVS-III; Ways of Coping Checklist-Revised (WCCL-R); Beck Depression Inventory-II (BDI-II); Beck Anxiety Inventory (BAI)	Alzheimer's support group participants; examined relationship between hardiness, coping strategies, & emotional distress	CG hardiness pos. related to problem-focused coping, support seeking; neg. related to wishful thinking, avoidant coping. CG hardiness predicted lower levels of dep.sxs.
Uthis, 2000	145; HIV CG's in Thailand	Face-to-face interview, caregiver Commitment Questionnaire (CCQ), Family Hardiness Index (FHI), AIDS Caregiver Scale(Satisfaction subscale)	Primary CGs living with HIV/AIDS pts.	High scores on commitment; family hardiness and coping predicted lower scores on neg. emotions & higher satisfaction in CG's.

In an unpublished dissertation, Henkle (1995) studied familial caregivers (N = 110) of homebound, functionally impaired, cognitively intact older adults. Using the FHI, Henkle found that caregivers who received the most benefit from caregiving had significantly higher family hardiness scores, felt less stress and threat, and were more resistant to the burden of caregiving. Conversely, caregivers scoring in the low range on the FHI had significantly higher appraisal scores for general stressfulness and threat, and found the caregiving situation difficult and burdensome.

In another unpublished dissertation using the FHI (Stevens, 1997), participants were elderly cerebral vascular accident patients and their primary caregivers (N = 80) while those patients were in their final stages of rehabilitation. The author examined family

hardiness and self-efficacy as coping factors. Stevens found a significant relationship between coping skills (family hardiness and self-efficacy) and affective responses for both caregivers and stroke patients. In her dissertation with primary caregivers (N = 145) cohabiting with the HIV+/AIDS patients they were caring for, Uthis (1999) used the stress and coping model of Lazarus and Folkman (1984) to conceptualize her study. Results indicated that caregivers using more emotion-based coping had an increased likelihood of negative emotions and report a higher level of caregiving stressors. Caregivers who had more problem-based coping tended to have a higher commitment to, and a greater satisfaction with, the caregiving role. Additionally, caregivers who appraised their stress as challenge, one of the three “C’s” of hardiness, used significantly more problem-based coping and had significantly higher satisfaction than other caregivers. Overall, high scores on commitment, family hardiness and coping predicted lower scores on negative emotions and higher satisfaction in caregivers.

Three studies used the HRHS (DiBartolo & Soeken, 2003; McKinney, 2000; O’Brien, 1994). In a journal article published in 2003 (DiBartolo & Soeken) participants (N = 72) were spouse caregivers of AD/HD patients dwelling in the community. The authors used a descriptive correlational design to examine the relationships among hardiness, appraisal, coping, and self-perceived health, with participants completing a mailed survey. The authors used Lazarus & Folkman’s (1984) model of stress and coping as the theoretical basis for their study, finding that hardier individuals were likelier to use problem-focused coping methods and have more positive appraisals of caregiving. Overall results indicated that hardiness moderated appraisal of caregiving challenges. The McKinney (2000) dissertation also used Lazarus and Folkman’s (1984) stress and coping

theory to identify predictors of depression, anxiety, and perceived health. Participants were a subset sample of family caregivers ($N = 31$) of cancer patients from a larger study. Results supported two primary tenets of the Lazarus & Folkman theory: individual appraisal of a situation influences adaptational outcomes; and personal resources may lessen the impact of situational stress. Hardiness emerged as a predictor of early depression, anxiety, and perceived health, and less hardy caregivers were found to be at risk for self-care disturbances. O'Brien (1994) also used the HRHS, examining hardiness, caregiver burden and psychological well-being in the self-selected family caregivers ($N = 59$) of frail elderly receiving assistance from the "Options for Elders" program. Results indicated that females and African-American caregivers had higher hardiness scores than males or Caucasians. There was a negative relationship between hardiness and burden, and a significant negative correlation between burden and psychological well-being.

The final three studies (Clark, 1996; Kulik, 2001; Matthews, 1995) concerning hardiness and caregivers used interviews to obtain their data. In a peer-reviewed publication, Clark used caregivers ($N = 53$) to relatives aged 65 and older to examine the effects of hardiness on caregiver distress, physical health, and appraisals of caregiving. Clark found that both hardiness and appraisals predicted psychological distress, but neither predicted physical health. In another publication, Kulik (2001) examined three aspects of spousal caregiving: commitment, perceived harmful effects, and delegating responsibility to others. Participants were elderly (mean age 59.3) Israeli female spousal caregivers ($N = 259$). Results indicated that women with high levels of emotional hardiness were less likely to delegate responsibility for caregiving. In an unpublished dissertation (Matthews, 1995) involving spousal caregivers ($N = 12$) of ADRD patients with difficult behaviors (wandering, aggression, paranoia, and sleep disturbance), participants were interviewed

twice at home and once by phone, using open-ended and semi-structured formats. Qualitative interview analysis revealed that caregivers viewed hardiness, social support, and reflective practice as important components in learning the caregiving role.

Summary

This section has reviewed the development of the scientific concept of hardiness, and reviewed the literature pertaining to hardiness and caregiving. Four of the studies reviewed involved caregivers of ADRD patients (Dibartolo & Soeken, 2003; Jensen, 1996; Matthews, 1995; Sussman, 2003). Although methodological issues, such as small sample sizes, lack of controlled studies, convenience sampling, and differing measures of hardiness were present, three of the studies reported a relationship between hardiness and appraisal of caregiving stress, with the tendency towards a positive relationship between hardiness and problem focused coping. The majority of the studies reviewed obtained results indicating that hardiness is a measurable concept; that it seems to have a negative relationship with caregiver depression, anxiety, distress, burden, and burnout; and seems to have a positive relationship with appraisal, problem-focused coping, and caregiver satisfaction.

Consequences of Immune Dysregulation

Infectious Disease

The quest to demonstrate causal relationships between psychosocial stressors and infectious illness has been conducted primarily in the laboratory by PNI investigators using subject inoculation by a vaccine or pathogen. This has been due to the simple statistical reality that infectious illnesses in the general population occur with relative

infrequency (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Alterations in low base rates become difficult to detect, especially when considering the time, expense, and small sample sizes typical of PNI research (Kiecolt-Glaser, et al., 2002). Thus, laboratory studies inoculating participants with a vaccine or a pathogen have several methodological advantages in infectious disease studies. For example, researchers may regulate dosage and exposure. Compared to naturally occurring infections, researchers may assess immune function pre-infection, thus obtaining improved data on causality (Kiecolt-Glaser, et al., 2002).

In two laboratory studies that compared spousal dementia caregivers to noncaregivers (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Vedhara, Cox, Wilcock, Perks, Hunt, Anderson, et al., 1999), the noncaregivers were significantly ($p = .02$; $p = .007$, respectively) more likely to show a clinically significant response to an influenza virus vaccine than the spousal caregivers. Another study compared antibody response to a pneumococcal vaccine over a 6-month period in dementia caregivers, noncaregivers, and former caregivers whose spouse had died. Results indicated that the antibody titers remained stable in the noncaregiver and former caregiver groups, but fell in the group of current dementia caregivers over the 6-month period (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000).

The idea that psychosocial factors can modulate a human response to a vaccine, in this case Hepatitis B, has been demonstrated by four different laboratories (Glaser, Kiecolt-Glaser, Malarkey, Kennedy, & Hughes, 1992; Jabaaij, Grosheide, Heijtkink, Duivenvoorden, Ballieyx, & Vingerhoets, 1993; Marsland, Cohen, Tabin, & Manuck, 2001; Petrie, Booth, Pennebaker, Davison, & Thomas, 1995). A prospective double-blind

study examined the relationship between infectious disease and negative affect utilizing a group of female subjects with no previous exposure to the rubella virus (Morag, Morag, Teichenberg, Lerer, & Yirmiya, 1999). Results indicated that at ten weeks post vaccination to a rubella virus vaccine, those with lower self-esteem and higher negative affect were more likely to have lower antibody titers. After inoculation with a rhinovirus, subjects who described having long-lasting interpersonal difficulties with friends or family were “substantially” more likely to develop a cold (Cohen, Frank, Doyle, Skoner, Rabin, & Gwaltney, 1998). The relationship between symptoms of infection and stress may be mediated by increased IL-6 production. In a study conducted by Cohen, Doyle, and Skoner (1999), both subjective reported symptoms and objective (as measured by mucus weight) symptoms of infection with the influenza A virus were associated with increased IL-6 production. Overall, these and other study results indicate that a delay in the immune response to the vaccine (or absent response) was correlated with individuals who were more anxious and more stressed (Kiecolt-Glaser, et al., 2002). Additionally, higher rates of clinical illness were also shown by adults demonstrating poorer responses to vaccines (Burns & Goodwin, 1990).

Cancer

Cancer is regarded as being composed of a heterogeneous group of diseases that have multiple etiologies (Anderson, Kiecolt-Glaser, & Glaser, 1994). As such, different cancers invoke varying degrees of immune system involvement. Lung cancer, which is influenced by chemical carcinogens, may be less influenced by behavioral, immunological, and psychological factors than immunogenic cancers associated with a virus (i.e., Epstein-Barr Virus: EBV) (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

Certain types of tumors, such as lymphoproliferative diseases in transplant patients, leukemias, Kaposi's sarcoma, and EBV-associated B-cell lymphoma in AIDS patients are associated with suppression of cellular immunity (Herberman, 2001). Once tumors have developed, the role of other cells of the immune system such as Natural Killer (NK) cells in resisting the metastatic spread and progression of those tumors is now strongly supported by research (Herberman, 2001). From a PNI perspective, the task is to establish clear links between tumor development, progression and psychosocial factors.

In order for that to occur, the "magnitude of immune dysregulation induced by behavioral and psychological factors must exceed the immune dysregulation associated with the malignant disease process and treatment" (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002, p.541). There is an impressive body of evidence that connects immune down-regulation and psychological stress; in particular, alterations in NK cell activity (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). In breast cancer patients, Anderson, Kiecolt-Glaser, & Glaser (1994) found that NK responses to cytokine stimulation and lower NK cell lysis were predicted by psychological stress. Complicating the picture, however, is the fact that while the immune system is most likely a primary line of defense against a subgroup of malignancies, many tumors do not stimulate an immune response since the immune system does not recognize them as foreign. Carcinogenesis may also be enhanced by the effect stress has on hormone production, changes in cellular DNA repair mechanisms, and possibly effects on apoptosis (Kiecolt-Glaser & Glaser, 1999c).

A trio of seminal studies lent support to the suggestion that group psychosocial interventions can help cancer patients cope more effectively, as well as help them live longer. The first study (Spiegel, Bloom, Kraemer, & Gottheil, 1989) was a ten-year

follow-up on the effects of a psychosocial group intervention on disease progression and mortality on patients (N = 86) with metastatic breast cancer. The original study (Spiegel, Bloom, & Yalom, 1981) was a one-year randomized prospective outcome study of the effects of a weekly support group for women with metastatic carcinoma of the breast. Patients were tested at four-month intervals. Results indicated that the intervention group (n = 50) had significantly lower scores on the mood disturbance scale of the POMS, fewer maladaptive coping responses, and were less phobic than the control group (n = 36). In the ten-year follow-up, Spiegel et al. found a significant difference in time of survival from randomization and intervention onset. The mean was 36.6 months (SD 37.6) for the intervention group and 18.9 months (SD 10.8) in the control group. Three patients remained alive, and death records were analyzed for the other 83. Plotting survival indicated that divergence in survival began at 8 months post-intervention, or the 20- month mark.

The second study was a randomized controlled intervention study (Fawzy, Fawzy, Hyun, Elashoff, Guthrie, Fahey, & Morton, 1993) that evaluated survival and recurrence of malignant melanoma in patients (N = 68) who had participated in a 6-week structured psychosocial group intervention 5 to 6 years earlier. Their results indicated that there was a trend for recurrence of the malignant melanoma, as well as a statistically significant greater rate of death in the control group as compared to the experimental group. In a ten-year follow-up study published in 2003, Fawzy, Canada, and Fawzy found that while the survival benefit of the intervention had weakened since the 1993 follow-up, it had not disappeared entirely. Participation in the original intervention group remained significant

for survival and, in fact, remained predictive of survival “even after controlling for the effects of other known prognostic indicators” (Fawzy et al., 2003, p102).

A recent replication study modified Fawzy’s structured psychoeducational group model for use with Danish cancer patients (N=262; Boesen, Ross, Frederiksen, Thomsen, Dahistrom, Schmidt, 2005). While survival data has not yet been obtained with this study, Boesen et al. did find a significant difference between the intervention group and the control group at the six-month follow-up on the Total Mood Disturbance score (TMD) of the Profile of Mood States (POMS). They also found significant differences in coping methods employed, with the intervention group using more of the active-behavioral and active-cognitive styles of coping than the control group, consistent with Fawzy et al. (1993) findings. The researchers concluded that the psychoeducational intervention devised by Fawzy et al. (1993) could be applied to patients from diverse cultures with beneficial effect on coping, albeit with culturally relevant modifications.

The third study (Richardson, Shelton, Krailio, & Levine, 1990) utilized a supportive educational intervention with patients (N = 94) newly diagnosed with hematological malignancies. Richardson et al. attempted to assess whether an educational intervention could affect compliance with the treatment regime of oral medication and scheduled clinic appointments, and if compliance in turn were related to survival. Patients were assigned at entry using a sequential cohort design into either a no-intervention control group (n = 25) or one of three educational program conditions: education and home visit (n = 22); education and shaping (n = 3); and education, shaping, and home visit (n = 24). Compliance with treatment was assessed with monthly self-report indices, abstracting medical records, and objective assessment of medication metabolite levels. Results

indicated that there were significant differences in survival ($p < .001$), clinic appointment compliance ($p < .01$), and medication adherence ($p < .05$) for the educational intervention versus the control group ($p < .001$). There were no significant differences between the three intervention groups on the dependant measures. Interestingly, Richardson et al. concluded that while there was a significant effect on prolongation of patient survival associated with the educational intervention, it was both due to, and independent of, the intervention effects on compliance.

A more recent study (Andersen, Farrar, Golden-Kreutz, Glaser, Emery, Crespin, et al., 2004) utilized a randomized controlled clinical trial design with women ($N = 227$) who were surgically treated for breast cancer. Researchers were examining the effects of a psychological intervention on mood, health behaviors, and immune function. They randomly assigned participants to either an assessment only group, or an intervention group that met once per week for four months. Sessions focused on strategies to alter health behaviors, reduce stress, improve mood, and maintain compliance to the prescribed cancer treatment and care regimen. Participants were re-assessed after intervention completion.

Results indicated that participants in the intervention group showed significant ($p < .05$) lowering of anxiety as measured by reduced scores on the anxiety scale of the Profile of Mood States (POMS), improved dietary habits, reduction in smoking, and improvements in perceived social support. Additionally, immune assays showed a significant difference between the intervention and assessment only groups ($p = .01$), with the intervention group immune responses either increasing or remaining stable, as evidenced by T-cell proliferation response to PHA and ConA. The assessment only group

showed a decline in both responses that was consistent across three concentrations of each immune assay.

Thus, the experimental evidence from these and other studies suggest that behavioral or psychosocial interventions designed to support, educate, and /or increase compliance with treatment regimes may influence hormone and immune function, in turn playing a part in influencing the initiation, and possibly the progression of cancer (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

Human Immunodeficiency Virus (HIV)

Disease progression and immunological change in people infected with HIV and their relationship to psychological variables has been a research focus. Greater concealment of homosexual identity has been associated with more rapid disease progression (Cole, Kemeny, Taylor, Visscher, & Fahey, 1996). Less cumulative social support over a five-year period, along with more cumulatively stressful life events, have also been associated with more rapid disease progression (Leserman, 1999). Slower decline in immune function, longer survival time, and later symptom onset have been linked to situational optimism about health outcomes among men with AIDS (Kemeny, 1994).

In additional studies Kemeny and her colleagues (Kemeny, 1994; Kemeny, Weiner, Duran, Taylor, Visscher, & Fahey, 1995) compared men who had experienced the death of one or more close friends as a result of AIDS in the prior year to men who had not. Their findings were replicated across two cohorts and indicated that lower numbers of CD+4 cells and increased expression of activation markers on lymphocytes were associated with higher levels of depressed mood in nonbereaved men, but not in bereaved

men. This finding led Kemeny to suggest that different processes were actually represented by higher depression scores in the two groups: depressed mood in the nonbereaved, grief in the bereaved. She suggested that the two processes have differing immunological correlates. Kemeny (1994) also found that a sharper decline in CD+4 cells was demonstrated by men who had been characterized by chronic and severe depression over a 2-year period, compared to nondepressed men matched on CD+4 levels and age at baseline.

Wound Healing

Unequivocally stated, “stress impedes wound healing, as well as some of the key immunological mediators in the early phases of wound repair, such as the proinflammatory cytokines” (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; p. 542). Statistically significant as well as clinically meaningful results have been found in studies of stress-related delays in healing of a standardized wound, with delays ranging from 24% to 40%, and effect sizes between .30 and .74 (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998). Additional research has suggested proinflammatory cytokine production in the local wound environment as a possible mechanism, with psychological stress having measurable negative consequences on that cytokine production (Glaser, Kiecolt-Glaser, Marucha, MacCallum, Laskowski, & Malarkey, 1999).

Distress prior to surgery has been shown to be associated with poorer performance on a number of outcome measures such as more postoperative complications, longer hospital stays, and higher rates of rehospitalization (Contrada, Leventhal & Anderson, 1994; Johnston & Voge, 1993). Thus, based on research from these and other studies,

clinically significant consequences could result from even small alterations in anxiety levels, through direct physiological mechanisms, or indirectly through decreased compliance with treatment regimes or increased pain (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998).

Autoimmune Diseases

In the case of autoimmune diseases, “a hyperactive immune response produces problems because it is unable to discriminate self from nonself and, as a consequence, attacks the body’s own tissues” (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; p. 542). While stress has been linked with both the exacerbation and the remission of symptoms, the processes are quite variable and not well understood (Rabin, 1999). In the case of multiple sclerosis (MS), researchers in a controlled study (Ackerman, Martino, Heyman, Moyna, & Rabin, 1998) compared patients’ and controls’ cytokine responses with a laboratory stressor. The study intent was to examine susceptibility of MS patients to stress-related exacerbations and investigate the possibility that individual differences in physiological and subjective responses to stress would underpin that susceptibility.

Although controls and patients stress responses did not differ, the authors felt that certain cellular immune responses potentially harmful to MS patients may be enhanced by psychological stress. In the context of inflammatory disease production, it has been hypothesized that disruptions in the communication between the brain and the immune system can produce such diseases as rheumatoid arthritis, major depression, and other affective disorders (Sternberg, Chrousos, Wilder, & Gold, 1992). In a 1998 study (Zatura, Hoffman, Matt, Yocum, Potter, Castro, et al.) that followed females (N = 20) with rheumatoid arthritis for a twelve-week span, clinician’s ratings of disease activity, T-cell

numbers, and soluble IL-2 receptors rose during an episode of increased interpersonal stress lasting seven days. Results indicated that subjects who reported more positive spousal interaction patterns and less spousal negativity or criticism did not display as large an increase in clinical symptoms.

Mechanisms of Action: How do psychological factors affect immune function?

One central gateway for psychological influences on health is the endocrine system (Rabin, 1999; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). The release of pituitary and adrenal hormones with concomitant multiple effects on immune system function can be provoked by stress and depression (Rabin, 1999). Key stress hormones, such as catecholamines and cortisol, have multiple immunomodulatory effects on immune function and can be elevated by social stressors (Glaser, & Kiecolt-Glaser 1994).

It has been noted as well that multiple health behaviors that increase risk for immune dysfunction, such as poor sleep, poor nutrition, less exercise, and a tendency for alcohol and drug abuse are more common among distressed individuals and that these health behaviors have both endocrinological and immunological consequences (Kiecolt-Glaser & Glaser, 1988). In particular, much of the release of growth hormone is stimulated by deep sleep. Growth hormone in turn is known to enhance a number of aspects of immune functioning (Veldhuis & Iranmanesh, 1996). Consequently, stressors that affect the sleep cycle can decrease growth hormone secretion. Researchers have shown that even partial sleep-loss one night can result in elevated cortisol levels the next evening (Veldhuis & Iranmanesh, 1996).

The most likely primary avenues by which psychological factors influence immune function are the endocrine system and health behaviors (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Other pathways have been identified; for instance, Sympathetic Nervous System (SNS) innervation of organs involved in the lymphatic system such as the spleen (Ackerman, Bellinger, Felten, & Felten, 1991). The cumulative long-term effects of the physiological responses to stress have been conceptualized as “allostatic load”, with the SNS and endocrine system playing a central role in this concept (McEwen, 1998). The SNS and the neuroendocrine system are viewed as primary mediators of the allostatic process in this conceptualization and play key roles in a spectrum of adaptive processes and harmful physiological outcomes (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; McEwen, 1998).

Laboratory studies of acute stress in humans have provided the strongest evidence to date implicating the SNS and the neuroendocrine system as primary mediators in immune change (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). In chronic stress, SNS and neuroendocrine mediation of immune changes may also exist. In Alzheimer’s caregivers, lymphocyte insensitivity to glucocorticoids resulting from chronically elevated cortisol levels has been reported (Bauer, Vedhara, Perks, Wilcock, Lightman, & Shanks, 2000), although demonstration of such mediation has not been found consistently in the literature.

Proinflammatory Cytokines

Interleukin-6 (IL-6)

In older adults, recent evidence has pointed to the dysregulation of proinflammatory cytokines as a central component in a number of diseases in that population. The proinflammatory cytokines are markers of chronic inflammation, and IL-6 has received particular attention (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). A number of researchers have found that distress and depression enhance the production of proinflammatory cytokines, IL-6 included (Dentino, Pieper, Rao, Currie, Harris, Blazer, et al., 1999; Lutgenforf, Garand, Buckwalter, Reimer, Hong, & Lubaroff, 1999; Maes, 1995, 1999; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993). Distress also provokes delays in wound healing, as well as enhanced risks for wound infection after injury (Rojas, Padgett, Sheridan, & Marucha, 2002).

Negative emotions may be an indirect contributor to proinflammatory cytokine overproduction and the consequent immune dysregulation. For example, anxiety or depression can either up- or down- regulate the secretion of proinflammatory cytokines, and directly affect the cells of the immune system (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

Interestingly, interleukin-2 (IL-2), an important defense against infection, may be implicated in the immunodepression of aging by the chronic, repeated, or slow-resolving infections or wounds that enhance secretion of proinflammatory cytokines and possible consequent inhibition of the IL-2 feature of the immune response (Catania, Airaghi, Motta, Manfredi, Annoni, Pettenati, et al., 1997). Taken as a whole, the evidence that stress increases the risks for extended-illness episodes and contagion, as well as

impairing the immune response to infectious challenges, is quite convincing (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

The population that stands to experience the greatest degree of change in immune system function, and consequently the greatest health risk, is the elderly. Increases in IL-6 production have been shown to be age-related (H. J. Cohen, 2000). A variety of conditions associated with aging, such as Alzheimer's disease, Type 2 diabetes, osteoporosis, arthritis, cardiovascular disease, periodontal disease, and certain lymphoproliferative diseases or cancers (multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia) have been linked to inflammation (Ershler & Keller, 2000). Additionally, chronic inflammation may be a key biological mechanism related to overall declines in physical functioning such as disability and frailty, ultimately leading to death (H. J. Cohen, Pieper, Harris, Rao, & Currie, 1997; Hammerman, 1999; Taaffe, Harris, Ferrucci, Rowe, & Seeman, 2000).

In a 1999 study, Ferrucci, Harris, Guralnik, Traci, Corti, Cohen, et al., found that future disability in older adults was predicted by elevated serum IL-6 levels. The authors speculated that this finding might be related to the pathophysiological role the cytokine plays in particular diseases, as well as the effects of the cytokine on muscular atrophy. In fact, Ferrucci and colleagues went even further and stated that "IL-6 may function as a global marker of impending deterioration in health status in older adults" (p. 645).

Interestingly, this seems to be true even past the point at which common risk factors such as obesity, hypertension, and cholesterol are less successful at predicting health deterioration among the very old (Ferrucci, et al., 1999).

Summary

This section of the literature review has covered the relationship of stress and the immune system in acute (laboratory), short-term, long-term, and chronic stress models. Special emphasis was placed on studies examining ADRD caregivers and immune dysregulation, in line with the focus of this study. This study was an attempt to enhance immune system functioning and reduce subjective stress levels in the familial caregivers of Alzheimer's disease and related dementia (ADRD) patients. In order to accomplish that objective, a controlled comparison between a cognitively based intervention and a no-treatment control group was conducted. The unique contribution of this study to the literature was in examining the effects of a cognitive behavioral stress management (CBSM) intervention on caregiver subjective distress and immune system functioning using IL-6 as a dependant measure of immune system function.

This study also attempted to contribute to the existing body of knowledge in the field of psychoneuroimmunology (PNI) by addressing the complicated inter-relationship between psychological stress and immune system functioning.

Psychosocial interventions and immune responses

A wide range of intervention strategies including cognitive-behavioral, exposure to a phobic stressor, relaxation, exercise, hypnotism, classical conditioning, self-disclosure, enhancing perceived coping and self-efficacy have been used with diverse populations.

Contexts and interventions most likely to influence immune function

Several factors need to be considered: first, the immune response shows relative insensitivity to psychological stress in some aspects (Herbert & Cohen, 1993), so

relationships may be difficult to demonstrate due to small effect sizes. Second, the performance and/or function of lymphocytes are more likely to respond to psychological stress and are therefore better choices for assay than simple lymphocyte counts or percentages. Additionally, the latter have less relevance for health (Herbert & Cohen, 1993).

Homeostasis needs to be taken into consideration as well. If the intervention is designed to enhance human immune system functioning, it could fail simply due to homeostatic regulation. Along similar lines, it should also be noted that enhancement of immune system functioning (absent any disease-, stress-, or age- related decline in the subject population) may in fact be undesirable, as an overactive immune system can lead to autoimmune disease (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). The length and scope of the intervention need to be considered as well. Generally, the shorter behavioral interventions with a narrower scope have yielded results that have been less impactful and enduring, in both the psychological and immunological arenas (Kiecolt-Glaser & Glaser, 1992; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Longer follow-up periods may have the advantage of showing changes not seen earlier (Fawzy, Fawzy, Hyun, Elashoff, Guthrie, Fahey, et al., 1993).

HIV+ gay men and psychosocial interventions

A series of studies (Antoni, 1997; Schneiderman, Antoni, Ironson, Klimas, Lapierre, Kumar, et al., 1994; Schneiderman, Antoni, Saab, & Ironson, 2001) involving HIV-positive but asymptomatic men used a 10-week cognitive-behavioral stress management (CBSM) and aerobic-exercise-training programs as interventions. Results indicated that

following notification of HIV seropositivity, both interventions buffered immune responses and distress responses.

In further studies with symptomatic gay men, positive results for mood and immune function were obtained with the CBSM intervention (Lutgendorf, Antoni, Ironson, Klimas, McCabe, Cleven, et al., 1997; Lutgendorf, Antoni, Ironson, Starr, Costello, Zuckerman, et al., 1998). Additionally, Antoni, Cruess, Cruess, Lutgendorf, Kumar, and Ironson (2000), using a 10-week CBSM intervention or a 10-week wait-list control, found significantly less urinary cortisol from CBSM (N=40) group participants than from controls. In conjunction with the series of studies listed above, this study also found that those positive results were maintained for 6 to 12 months following the intervention and that the reductions in distress seemed to be mediated by alterations in social support and coping related to the intervention. Involvement of various components of the neuroendocrine system as mediators of immune cell function, associated with the CBSM, was demonstrated as well (Antoni et al., 2000; Schneiderman et al., 2001).

Another study utilized a 10-week CBSM intervention to assess the effect on immunoglobulin G (IgG) antibody titers to herpes simplex virus type 2 (HSV-2). In a population of HIV+ gay men (N=62), subjects were randomly assigned to either the CBSM intervention or a wait-list control condition. Results indicate that HSV-2 IgG titers were significantly reduced in the CBSM group but remained unchanged in the control group after the 10-week intervention period. Additionally, lower mean stress levels achieved after home relaxation practice were associated with greater decreases in HSV-2 IgG among CBSM subjects (Cruess, Antoni, Cruess, Fletcher, Ironson, Kumar, et al., 2000).

Disease development and suppression of emotion

A link between development of physical disease and suppression of strong emotion has received support from several researchers. They have reported finding immunological differences between participants who disclosed upsetting or traumatic events and those who were nondisclosers (Christensen, Edwards, Wiebe, Benotsch, McKelvey, Andrews, et al., 1996; Esterling, Antoni, Fletcher, Marguiles, & Schneiderman, 1994; Petrie, Booth, Pennebaker, Davison, & Thomas, 1995).

In the Christensen et al. study (1996), male undergraduates (N = 43) classified as either high or low hostility on the Cook-Medley Hostility Scale were randomly assigned to either a verbal self-disclosure (VSC) or a nondisclosure discussion (DC) condition. Change in NK cell activity was measured after an experimental task. Results indicated a significant interaction between DC and hostility. In the VSC condition, high hostility participants demonstrated a significantly greater increase in NK cell cytotoxicity compared to low hostility participants. Researchers speculated that the enhanced NK cell cytotoxicity was correlated to a more pronounced acute arousal response to the experimental task for the high hostility VSC participants.

In the Esterling, Antoni, et al. study (1994), Epstein-Barr virus (EBV) seropositive undergraduates (N = 57) were randomly assigned to one of three conditions: write about stressful events, talk about stressful events, or write about trivial events. Baseline measures of EBV were taken. Subjects had three 20-minute sessions within one week; blood samples were then drawn again. Significant differences were found between all three groups on levels of EBV titers. Subjects in the verbal/stressful group had significantly lower EBV titers (with EBV, lower antibody titers suggests improved

immune function) compared to the written stressful group, which had significantly lower EBV antibody titers compared to trivial/written group. Researchers performed a content analysis, which indicated that the verbal/stressful group achieved the greatest improvements in cognitive change, self-esteem, and adaptive coping strategies.

Petrie and colleagues (1995) examined whether the immune response to a Hepatitis B (Hep B) vaccination program could be influenced by writing about personal traumatic events. Subjects were medical students (N = 40) randomly assigned to write about events that were personally traumatic or control topics over four consecutive daily sessions. Subjects received their first Hep B vaccination after completion of the intervention, with booster injections at one and four months after the intervention. Results showed a significantly higher level of antibodies against Hep B in the emotional expression group than in the control group at the four and six-month follow-up periods.

The results of the above studies provide support for a link between emotional disclosure and health; however, the degree of emotional and cognitive involvement in the disclosure process, coupled with reduction of stressful topic avoidance and traumatic event meaning reorganization, may affect the benefits of disclosure based intervention (Esterling, Antoni, et al., 1994; Lutgendorf, Antoni, Kumar, & Schneiderman, 1994).

Classical conditioning of the immune response

A number of studies have demonstrated classical conditioning of the immune response in animals; however, similar studies with humans have been rare (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). There may be data from cancer research to support classical conditioning of immune suppression during chemotherapy (Bovbjerg, Redd, Maier, Holland, Lesko, Niedzwiecki, et al., 1990). Specifically, Bovbjerg and

colleagues found that after controlling for possible increases in anxiety, blood samples drawn at home from women undergoing treatment for ovarian cancer (N = 20) several days prior to in hospital treatment showed immune suppression compared to those drawn in the hospital immediately prior to treatment. Nausea became a conditioned response in anticipation of treatment as well.

Hypnosis

Results from studies employing hypnotic intervention have been mixed. The “double arm” technique has been the basis of the more well-designed and controlled studies. In this paradigm, participants were injected with the same antigen in both arms, and had suggestions made to them that only one arm would show changes characteristic of immediate and/or delayed hypersensitivity reactions (i.e., swelling, itching, burning, wheal, erythema). Locke, Bernard, Zachariae, Francine, Tollins, Covino, et al. (1994) found no effects in their study employing the “double arm” technique, while Kiecolt-Glaser & Glaser (1992) report positive findings from several studies.

Several issues remain to be addressed in resolving the question of the cause of intervention effects, among them the use of specific-immune related imagery and suggestions, relaxation techniques and general effects of a relaxed state, and participant hypnotic susceptibility (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

Studies using relaxation interventions

Relaxation has been utilized as a component in a number of CBSM interventions (Antoni et al., 2000; Cruess, et al., 2000; Lutgedorf, 1997, 1998). However, there are no published studies in the ADRD caregiving literature using relaxation as a stand-alone intervention. Kiecolt-Glaser, Glaser, Williger, Stout, Messick, Sheppard, et al., (1985)

conducted a study assessing the enhancement of immunocompetence in geriatric residents (N = 45, mean age = 74) of independent living facilities. The study utilized relaxation and social contact interventions. Subjects were randomized to a relaxation training group, social contact, or no social contact. Blood samples were drawn from the subjects at baseline, at intervention completion one month later and at follow-up one month post intervention. Immune measures used were NK cell activity, antibody titers to HSV, and lymphocyte response to mitogen stimulation (PHA and PWM). Subjects in the relaxation group met with a study investigator 3 times a week for approximately 45 minutes for one month. Results on psychosocial measures were significant for the relaxation group on measures of distress at the end of the intervention compared to baseline and the follow-up compared to end of the intervention. There was a significant ($p < .01$) increase in subject's self-rated sleep quality, with no significant effect by group. On the immunological measures, the relaxation group showed a significant change between baseline and intervention completion and intervention and follow-up on NK cell activity and HSV antibody titers. The authors concluded, "it is therefore possible that the long-term practice of relaxation might provide important immunological benefits" (p. 36).

Dementia Caregivers and Immune function

There are very few studies utilizing psychosocial interventions and immune function dependent variables with ADRD caregivers. In 2003, Grant, McKibbin, Taylor, Mills, Dimsdale, Ziegler, et al. tested the efficacy of an in-home respite intervention at reducing markers of SAM activation and psychological distress. Subjects were spousal caregivers

(N = 55), 27 of whom received the respite and 28 who were wait-listed. Plasma catecholamine levels were tested before and after the 2-week respite intervention. Results showed that plasma epinephrine declined significantly in the respite group, and rose in the wait-list group.

In a 2002 study, Garand, Buckwalter, Lubaroff, Tripp-Reimer, Frantz, and Ansley employed the progressively lowered stress threshold model (PLST) in a controlled intervention with ADRD caregivers (N = 39). The PLST intervention is based on the assumption that persons with ADRD exhibit a progressive deterioration in their ability to respond to and interact with the environment appropriately. Results did not support the hypothesis that PLST enhanced immune performance, although small sample size may have limited power to detect differences.

Wilkins, Castle, Heck, Tanzy, and Fahey (1999) used an 8-week structured psychoeducational intervention to assess T cell proliferation response to PHA. Subjects were 11 female ADRD caregivers (mean age 70) and matched controls. Results indicated that experimental subjects showed a decline in immune function over the eight weeks of the intervention, while controls showed no decline. However, one-month follow-up revealed an improving trend in T cell proliferation to PHA, indicating an enhanced immune response.

Hosaka and Sugiyama (2003) used five 90-minute sessions of a modified group structured intervention with 20 female ADRD caregivers. Even though only 5 of the 20 caregivers reported themselves as healthy, a significant augmentation of NK cell activity occurred. Vedhara, Bennett, Clark, Lightman, Shaw, Perks, et al. (2003) used a CBSM

intervention with spousal ADRD caregivers (N = 43), attempting to enhance antibody responses to an influenza vaccination. Caregivers were allocated to an 8-week CBSM (N = 16) or a non-intervention condition (N = 27). There were 27 non-carer controls for a no-treatment group. Antibody titers were measured at baseline, 2, 4, and 6 weeks post-vaccination. Results demonstrated that 50% of the experimental caregivers group produced a four-fold increase in antibody titer, compared to 7% of the non-intervention carers and 29% of the non-care controls.

Wilcox, King, Vitaliano, & Brassington (2000) used a four-month moderate intensity exercise program in 23 family caregivers randomized to the experimental or wait-list control condition. NK cell activity was the immunological variable of interest. Results showed that group assignment was unrelated to NK activity.

In a study (Irwin, Pike, Cole, & Oxman, 2003) that used non-caregiving, community-dwelling older adults as participants (N=36), a behavioral intervention consisting of 15-weeks of Tai Chi Chih, 3 times per week, was administered. Participants were randomized to an experimental group (n = 18, mean age = 70.9) or a wait-list control group (n=18, mean age = 70.1). The dependent measure was varicella-zoster virus (VZV) specific cell-mediated immunity (CMI). Results indicated that VZV-specific CMI increased by 50% from baseline to 1-week post-intervention in the experimental group ($p < .05$) and was unchanged for the control group.

Psychosocial Interventions for ADRD caregivers

The most recent reviews of psychosocial interventions for ADRD caregivers (Cooke, McNally, Mulligan, Harrison, & Newman, 2001; Kneebone & Martin, 2003; Schulz,

O'Brien, Czaja, Ory, Norris, Martire, et al., 2002) have come to similar conclusions. Overall, although many studies reported small to moderate significant effects on a broad range of outcomes, only a small proportion of these studies achieved clinically meaningful outcomes.

However, the consensus is that caregiving intervention studies have increasingly shown promise of affecting public health outcomes in areas such as service utilization, including delayed institutionalization; psychiatric symptomatology (including the successful treatment of major and minor depression) and providing services that are highly valued by caregivers. It is noted that caregiver interventions may require a delay before their effects are apparent, and that studies that fail to incorporate follow-up assessments may miss clinically significant results (Cooke et al, 2001).

Sorensen, Pinquart, and Duberstein (2002) conducted a meta-analysis on caregiver intervention efficacy and concluded that caregiver interventions are effective. Significant improvements ranged from .14 to .41 standard deviations in the areas of caregiver burden, depression, subjective well-being, perceived caregiver satisfaction, knowledge, and care receiver symptoms. A wide diversity of dose and intensity is represented across the interventions, ranging from two clinic visits to a year of daily access to clinicians. Other methodological problems are cited by reviewers, such as: sample sizes too small to detect even large effects (Cooke, et al, 2001); a genuine paucity of randomized controlled clinical trials, often with incomplete implementation (Schulz, et al., 2002); poorly described interventions, with data on treatment implementation not collected or reported; and lastly, a small proportion of studies reporting clinically significant outcomes (Schulz, et al., 2002; Cooke, et al., 2001; Kneebone & Martin, 2003).

The next section of the literature review focuses on the caregiver intervention literature in the areas most relevant to the themes of this study: interventions using cognitive-behavioral techniques with or without relaxation components, familial ADRD caregivers as participants, and/or employing controlled, randomized clinical trials designs. The review will start with a description of the REACH project, a multi-site, multi-intervention study designed to address a number of the methodological issues in the caregiving literature. REACH was designed as a randomized, controlled clinical trial, encompassing six different sites, 1,222 caregiver-care-recipient dyads, and spanning five years from conception to completion.

Resources for Enhancing Alzheimer's Caregiver Health (REACH)

The most comprehensive study of psychosocial interventions for carers of people with dementia published since the Cooke et al. (2001) review is the REACH project. REACH was specifically designed to test promising interventions for enhancing the support for family caregivers and thus the quality of caregiving, for those engaged in caring for a family member suffering from Alzheimer's disease and related dementias (ADRD). It was a 5-year program, originally funded in 1995 by the National Institutes of Health (NIH) and currently sponsored by the National Institute on Aging and the National Institute for Nursing Research.

Six intervention sites and a coordinating center were originally funded, with the purpose of developing and investigating "interventions for family caregivers of individuals at the moderate level of impairment" (Burgio, et al., 2001, p. 483). A particular focus of the REACH program was to address at least two issues in caregiving

research: examine the caregiving experience of minorities by including substantial minority participation; and develop standardized outcome measures to facilitate comparisons of efficacy across populations and interventions (Burgio, et al., 2001).

Additionally, REACH was designed to address four additional methodological issues in the extant intervention literature: (1) even large effects are difficult to detect due to small sample sizes; (2) infrequent use of randomized controlled trials and inappropriate implementation when used; (3) poor intervention description and data on treatment implementation uncollected or unreported; and (4) poor representation of minority populations (Wisniewski et al., 2003).

In a series of articles published between 2001 and 2003, study characteristics (Wisniewski, et al., 2003), treatment implementation (Burgio, Corcoran, Lichstein, Nichols, Czaja, Gallagher-Thompson, et al., 2001), methodological issues (Wisniewski, Belle, Coon, Marcus, Ory, Burgio, et al., 2003) and results (Gitlin, Belle, Burgio, Czaja, Mahoney, Gallagher-Thompson, et al., 2003), were discussed and analyzed.

Recruitment and Eligibility criterion

In order to be eligible for participation, REACH subjects had to be over the age of 21, living with and providing care for a relative, significant other, or personal friend for a minimum of 4 hours per day for at least the past 6 months. If caregivers had been involved in another caregiver intervention study, or had an illness that would prevent them from participation in the present study for a six-month minimum, they were excluded. Logistical requirements included having a telephone, planning to remain in the geographic area for at least six months and competency in languages specified at each study site.

The care recipients had to have a medical diagnosis of probable ADRD or a Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) score of 24 or lower, indicative of at least moderate cognitive impairment. Care recipients had to have a minimum of one limitation in their activities of daily living (ADLs), or a minimum of two dependencies in their instrumental activities of daily living (IADLs; Lawton & Brody, 1969).

Study population characteristics

There were 1,222 participant dyads in the REACH study (1,222 caregivers and 1,222 care recipients). All caregivers were familial caregivers. Overall, the sample (mean age 62.3 yrs, SD = 13.6 yrs) was 18.6% male, 56.4 % Caucasian, 24% African-American, 19% Hispanic/Latino; 48% of the caregivers were spouses, 44% were children, 2% were siblings, and the remaining 6% a combination of nieces, nephews, and grandchildren. In order to provide care, 40% of the caregivers had begun living with the care recipient. 57% of the caregivers had greater than a high school education, and about 19% had less than a high school education.

The mean Center for Epidemiologic Studies-Depression (CES-D; Radloff, 1977) score in caregivers was 15.4 (SD = 11.5). The CES-D has a range of 0-30, and scores above 16 are often used as an indicator of risk for clinical depression. Self-reported levels of caregiver depression and burden were similar to that published in the majority of caregiver intervention studies (Wisniewski, et al., 2003). Caregivers reported care recipients health to be poor (18%); fair (30%); good (14%); very good (14%), and excellent (8%). The average Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) score was 12.6 (SD=1.3). The range on the MMSE is 0-30, and lower

scores indicate greater cognitive impairment. The number of behavior and memory problems noted by caregivers on the revised Memory and Behavior Problems Checklist (RMBPC; Teri, Truax, Logson, Uomoto, Zarit, & Vitaliano, 1992) was 10.2 (SD = 4.2; range = 0-24); of 6 activities of daily living (ADLs; Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963) care recipients were impaired on an average of 3.3 (SD = 2.1); and on instrumental activities of daily living (IADLs; Lawton & Brody, 1969), care recipients scored an average of 7.3 (SD = 1.3) out of a possible 8 .

Overall, caregivers were moderately burdened and distressed and care recipients demonstrated moderate to high levels of impairment. Once again, these results are similar to those reported in other caregiving studies (Wisniewski, et al., 2003).

Study sites

There were six different sites where the study was conducted. Birmingham (N = 140) was a home-base problem solving and behavioral skills training. In

Boston (N = 100) a telephone-based system offered support and advice via voice mail. Memphis (N = 245) used a primary care system, providing training in behavior and stress management. Miami (N = 225) used a multi-system, family-focused intervention, integrated with a computer-telephone interface and home-based intervention.

Philadelphia (N = 255) used home-based behavioral and environmental skills training.

Palo Alto (N = 257) used group-based coping skills training and enhanced support.

All sites conducted an initial telephone screening and baseline, 6, 12, and 18- month post baseline in-person interviews; all sites used a control condition, recruitment, and standardized study materials. Study procedures were tailored at each site to the specific racial or ethnic group being served (specifically to be sensitive to SES, educational level,

cultural belief system and ethnic background), interventionist and caregiver were matched for race and/or ethnicity where possible, the intervention was implemented in community settings where possible, and interviewers and interventionists received cultural sensitivity training before working in the field.

Intervention details by site:

Birmingham

Birmingham used the Skills Training Intervention (STI), which was designed to “help African-American and Caucasian caregivers manage both the stress and distress of their caregiving situations” (Wisniewski et al., 2003; p. 378).

STI had two components: caregiver-focused problem solving training and care-recipient focused behavior management skill training. Interestingly, the care-recipient component taught caregivers better techniques for addressing patient behavioral excesses and deficits that contribute to caregiver stress. The caregiver problem solving skills training focused on reducing caregiver stress by increasing their ability to cope through strategies such as engaging in positive health behaviors and increasing pleasant social activities. Intervention training began with one group workshop offered at local community sites followed by six in-home visits in the eight weeks following the workshop. Five bimonthly home visits then alternated with bimonthly therapeutic phone contacts.

Palo Alto

The Palo Alto site conducted two interventions, both specifically targeted towards Caucasian and Hispanic women: Coping with Caregiving (CWC) and Enhanced Support Group (ESG).

CWC is a class-based psychoeducational intervention, set up as small, interactive classes that are designed to teach several skills for mood-management that help alleviate caregiver distress and reduce the actual stress associated with caregiving. Two key instructional ideas are actively integrated into the classes. First is reducing negative affect via instruction in relaxation techniques, assertive communication and realistic appraisal of care recipient behavior. Second, increasing positive mood states via instructing caregivers to see the relationship between mood and activities, increasing everyday pleasant activities, setting goals and rewarding accomplishments.

ESG is essentially a support group, based on research (Cobb, 1976; Dean & Lin, 1977; Finch, Okun, Barrera, Zatura, & Reich, 1989) showing that the quality of one's support network can have a strong moderating or buffering effect on the impact of stress. ESG is not manualized in the detail that CWC is and attempts to address a lack in the literature regarding well-designed empirical studies on the helpfulness of caregiver support groups. ESG is "enhanced" in that a group of identified caregivers are gathered together and encouraged to commit to regular attendance at a professionally led support group for one year.

Philadelphia

Philadelphia used the Environmental Skills Building Program (ESP), a standardized, 20-week psychoeducational program. ESP focused on educating caregivers on the relationship the environment can have on care recipients behavior as well as the overall impact of the environment on people with ADRD. As care recipient behavior deteriorates due to disease progression, maladaptive behavior (e.g., resistance to ADL's) can occur as a result of the demands of unchanging tasks and objects.

ESP describes four layers that can be adjusted to resolve the discrepancy between the ADRD person's capabilities and environmental demands. They are a physical dimension (objects); a task dimension (daily routines); a social dimension (household composition and social resources); and a cultural dimension (shared values and beliefs).

The intervention is a client-driven, home-based service with caregivers being taught how to identify and prioritize problems, then brainstorm and implement solutions, thus reducing behavioral stressors in the environment. Ultimately, the caregivers are provided the tools they need to reduce caregiver burden and strain.

Miami

The Miami site used Family-based Structural Multisystem In-home Intervention (FSMII), an intervention focused on both Cuban American and Caucasian families. It comes from the work of Szapocznik, Kurtines, Perez-Vidal, Jervis, and Foote (1989), and is a therapy-based intervention.

FSMII attempts to identify existing problems in communication and facilitates changes in the patterns of interaction between family members and caregivers. It utilizes a family systems approach that encourages caregivers to more effectively manage existing family and community resources, and to gather more of the same. Key FSMII goals are: reduction of caregiver distress fostered by living with and managing a family dementia sufferer; and improvement of overall caregiver and family functioning.

The FSMII system was expanded by utilizing a Computer-Telephone Integrative System (FSMII+CTIS), the rationale being "computer and communication plus technologies can be used effectively to facilitate communication linkages established in therapy sessions" (Wisniewski et al., 2003, p.379). CTIS also incorporated three other

functions: informational, with links to nutrition and medication information as well as other resource sites; orientation material and memos for the receiver of care; and caregiver respite, in which activities, material, and family vignettes can be used to help occupy the care recipient.

Memphis

The Memphis site used three interventions, all based on the stress and coping model of Lazarus and his associates (Folkman, Schaeffer, & Lazarus, 1979; Lazarus & Folkman, 1984; Lazarus & Launeir, 1978).

The model uses educational interventions to help the caregiver learn to assess their own ability to cope with the rigors and demands of their caregiving in a more efficacious manner. All three interventions worked with caregivers on a one-to-one basis, sharing educational material and caregiver information, and exploring the provision of caregiver support within a primary care setting.

Information and Referral (IR) was intended to simulate the “usual level of care” for ADRD caregivers. At study entry, caregivers received telephone numbers for local and national ADRD organizations and commercial educational pamphlets about dementia and associated topics in conjunction with a primary care office visit. This occurred four to six times per year during regularly scheduled ADRD office visits.

Behavior Care (BC) built on the IR materials and information, adding an individual counseling session and written material focused on behavior management of the care recipient. Caregivers were also taught personal coping strategies in the event of problem behaviors.

Enhanced care (EC) built on both IR and BC by teaching stress and behavior management strategies specifically designed for the caregivers themselves. EC focused on successful cognitive and behavioral strategies for changing negative thinking patterns, and incorporated relaxation training as well. The intervention was both stepped (IR → BC → EC) and hierarchical, with each component building on the preceding one.

Boston

The Boston site used a telephone-based intervention known as Telephone-Linked Computer (TLC). The intervention was one year in length, and focused on reducing caregiving stress in caregivers. TLC was designed to function with Hispanic, African American, and Caucasian caregivers, as well as other ethnic minority caregivers.

TLC's design was strongly influenced by a conceptual model of Alzheimer's caregivers' stress developed by Pearlin, Millan, Semple, and Skaff (1990). The model proposes that the caregiver's social and personal resources can mediate the level of caregiver stress. Caregiver stress takes into account those stressors related to caregiver SES, personal history and care recipient cognitive level and behavior. The typical main outcomes of caregiver stress, such as physical limitations, mental health symptoms, and surrender of caregiver activities, can be positively altered using TLC. The telephone computer link provided a 24 hour/day, computer-controlled human voice available to speak with caregivers at home. TLC also included a voicemail caregiver support network with a voicemail bulletin board and e-mail to other caregivers for advice, support, and information. Thus, the sense of social isolation not uncommon among caregivers was reduced. TLC had two additional features: voicemail access to a geriatric nurse specialist

and an activity/distraction option in which the system would conduct a twelve-minute conversation with the care recipient to provide a brief respite for the caregiver.

Intervention group assignment

Assignment to a group occurred after completion of the baseline battery. Allocation procedures varied from site to site for study design and logistical reasons. The goal at each site in assigning participants was the same: to assure that the distributions of measured as well as unmeasured characteristics were balanced across intervention groups.

Birmingham used a minimization procedure that balanced an a priori defined characteristic profile of race, severity of behavior disturbance, and severity of cognitive impairment. Participants were assigned to the intervention that needed that participant characteristic profile to balance the interventions.

Boston separated caregivers by gender and randomly allocated between both intervention groups in balanced blocks of randomly selected sizes of six or eight (after 6 or 8 participants enrolled, 3 or 4 would be in each intervention).

Memphis used the technique of “blocked randomization,” in which stratification by gender in blocks of six was used. Miami stratified by gender and ethnicity of the caregiver.

The Palo Alto site had restricted enrollment to female caregivers, and stratified randomization based on the ethnicity of the caregiver. Caregivers were then asked their primary language (English or Spanish), and which locations, days, and times they could meet for their intervention. Once four participants were identified who had the same primary language and could meet at the same location, day, and time, they were

randomly assigned to an active intervention (probability .70) or the control condition (probability .30). Once the group was assigned, if they had been assigned to an active intervention, up to seven more participants were then recruited for that language, location, day and time, and then randomly assigned to one of the two active interventions.

REACH results

While much of the data gathered from the REACH study has yet to be published, there has been at least one article published describing study results. Gitlin and colleagues (2003) used meta-analysis to examine pooled parameter estimates of 9 active treatments compared with 6 control conditions. Data were taken from the 6-month point of the study on caregiver burden and depressive symptoms. Additionally, the associations between caregiver characteristics and outcomes were examined.

Overall results indicated that active interventions were significantly ($p = .022$) better than control conditions at reducing caregiver burden as measured by scores on the Revised Memory and Behavior Problems Checklist (RMPC) Burden scale. Active interventions showed themselves to be superior to control conditions for caregivers with lower levels of education (high school or less) and for women.

On depression as measured by the CES-D at the six-month mark, a statistically significant association of group assignment at the Miami site was found for the family therapy and computer technology intervention ($p = .034$). There were no statistically significant differences between active and control groups for either the men or women on the 6-month CES-D scores at any of the other sites.

In terms of race, there were no statistically significant differences between active and control group conditions for African-American, White, or Hispanic caregivers on burden scores. However, on 6-month CES-D scores, while there were no statistically significant differences between active and control group conditions for White or African American caregivers, Hispanic caregivers showed active interventions superior to control conditions, as did nonspouse caregivers and caregivers with less than a high school education. Gitlin et al. (2003) commented that while REACH “set new standards” (p. 371) regarding application of randomized clinical trial methodology, it was only “somewhat successful in achieving clinically meaningful outcomes” (p. 371).

Interestingly, unpublished data from REACH affirms social validity in that the study participants consistently rated interventions as more helpful, beneficial, and valuable than control conditions. However, outcomes with public health significance are not supported by the data. A closer examination of the CES-D scores (Gitlin et al., 2003) suggest that the interventions did benefit those caregiving groups identified by the researchers as being most in need of support: Hispanic, with language and other barriers in accessing support services; those caregivers who were not spouses of the care recipient; and those caregivers who were less educated.

Ultimately, the results of REACH confirm what multiple reviews of the caregiving literature have concluded. While study participants consistently rated interventions as beneficial, and some clinically meaningful outcomes were achieved, there is no single, consistently effective, easily implemented method for eliminating the multiplicity of stressors faced by the multiple types of familial dementia caregivers.

Non-REACH Psychosocial caregiver intervention studies

In a randomized controlled trial, Hebert, Leclerc, Bravo, Girouard, and Lefrancois (1994) attempted to measure the efficacy of a support group program designed to alleviate the burden for caregivers of ADRD patients.

Forty-one caregivers were randomly assigned to either a study ($n = 23$) or control group ($n = 18$). Subjects in the study group attended eight meetings of a structured program for two hours each session. The sessions consisted of psychoeducation, role-playing behavior management issues, learning stress management techniques, and discussion of the emotional impact of caregiving. Control group subjects were referred to Alzheimer society meetings. All subjects were evaluated at baseline, 8 weeks, and 8 months. Dependent variables were the Burden Interview, RMBPC, Brief Symptom Inventory (BSI), and Alzheimer's disease Knowledge Test. Compared with controls, study subjects had a significant increase in knowledge ($p < 0.0001$) but no significant difference on any other outcome variables. Results seem to indicate this type of support group program has minimal impact on caregiver morbidity and burden.

In another randomized clinical trial, Mohide, Pringle, Streiner, Gilbert, Muir, and Tew (1990) constructed an intervention of family caregiver support to aid in the home management of ADRD patients by familial caregivers. Thirty caregivers were randomized to the intervention; thirty control participants to community nursing care.

The intervention consisted of caregiver-focused health care, regularly scheduled in-home respite, assistance with problem solving, and a self-help family caregiver support group. Measures used were the CES-D and the state-anxiety portion of the State-Trait inventory. Measurements were taken at baseline, midway (3 months), and completion

(6 months). Results indicated that caregivers scored higher at baseline on the CES-D than the general population, but not in the moderate or high range. However, more than 50% of those who completed the trial were at or above the CES-D cutoff point of 16, indicating possible depressive symptomatology. There were no significant differences found between groups on the study measures; however, there was a general trend in the experimental group towards an improved quality of life, delayed long-term institutionalization of their care recipients and increased consumer satisfaction with nursing care.

Zarit, Anthony, and Boutselis (1987) compared two interventions (family counseling and support groups) with ADRD caregivers to assess their efficacy in relieving caregiver stress and burden.

Both treatments were designed to implement features of a three part stress-management model that has been identified in prior research with caregivers. First, providing information about the patient's disease and its effects on behavior; second, teaching behavioral problem-solving for managing difficult behavior; and lastly identifying potential support for caregivers. Two sites in differing geographic areas were used in the study and subjects were randomized to treatment or control group at each site. Each site ran only one intervention (family therapy or support group); each intervention lasted 8 sessions. While subjects in the treatment groups made gains, there was no significant difference between groups, although treatment gains were maintained at the one-year mark.

Marriott, Donaldson, Tarier, & Burns (2000) conducted a prospective single-blind randomized controlled trial (N = 29) comparing an experimental group that received a

14-session cognitive-behavioral family intervention with 2 control groups with a 3-month follow-up. Sessions were two weeks apart.

The primary hypothesis was that family intervention would reduce the burden of care in caregivers, as measured by indices of psychological distress and depression compared to management as usual. Subjects were randomly assigned to one of three groups: family intervention ($n = 11$) or either one of the two control groups ($n = 9$, $n = 9$). Results showed there were significant ($p < 0.01$) reductions in distress and depression in the intervention group compared with control groups at post-treatment and follow-up. There were significant ($p < 0.024$) reductions in behavioral disturbance at post-treatment and an increase in activities at 3 months in patients in the intervention group. Results suggest that family intervention can be efficacious for caregivers of patients with AD, and have a positive impact on patient behavior.

Summary

Differences in perceptions of an event, as well as reactions to that same event, can provoke different endocrine and immune responses (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). The type of interpretation and response rendered by the individual to the environment determines their responses to stress. It also has influence on health behaviors, contributes to the neuroendocrine and immune response, and may ultimately affect health outcomes. The chronic stress associated with ADRD caregiving has been associated with widespread immune dysfunction. Affected functions have included diminished NK cell activity, reduced memory T- cell response to Herpes Simplex virus Type I, poorer antibody response to influenza virus vaccine, shortened duration of the

IgG antibody response to a pneumococcal bacterial vaccine, and increased circulating IL-6 levels (Yang & Glaser, 2002). In fact, research indicates that the immune consequences related to the chronic stress of caregiving persist long after caregiving has ended (Yang & Glaser, 2002).

Interventions in health psychology are designed to enhance and improve health behaviors and modulate the stress response by teaching individuals more effective coping responses, as well as adaptive methods of interpreting and responding to life challenges (Lutgendorf & Costanzo, 2003). Thus, this study attempted to further investigate the impact of stress-reducing interventions on psychological and immune function by conducting a controlled comparison between a cognitive behavioral stress management (CBSM) psychosocial intervention and no-treatment control group. Reduction in caregiver stress was measured by scores on the Center for Epidemiological Studies-Depression (CES-D), Profile Of Mood States (POMS), and Personal Views Survey-III-Revised (PVS-III-R). Immune system function was measured by plasma levels of IL-6.

Hypotheses

This study was an attempt to enhance immune system functioning and reduce subjective stress levels in the familial caregivers of Alzheimer's disease and related dementia (ADRD) patients. In order to accomplish that objective, a controlled comparison between a cognitively based intervention and a no-treatment control group was conducted. The unique contribution of this study to the literature was in examining the effects of a cognitive behavioral stress management (CBSM) intervention on

caregiver subjective distress and immune system functioning using IL-6 as a dependant measure of immune system function.

This study also attempted to contribute to the existing body of knowledge in the field of psychoneuroimmunology (PNI) by addressing the inter-relationship between psychological stress and immune system functioning.

Based on the literature review, the following hypotheses are made for the current study:

Hypothesis I

The cognitive-behavioral stress management (CBSM) group will improve the well-being of the familial caregivers as evidenced by:

Ia: A significantly greater decrease in mean CES-D scores by comparison to the control group.

Ib: A significantly greater decrease in mean TMD of the POMS scores by comparison to the control group.

Ic: A significantly greater increase in mean HardiAttitude scores by comparison to the control group.

Id: A significantly greater decrease in plasma IL-6 concentrations by comparison to the control group.

Ie: A significantly greater decrease in mean POMS Tension-Anxiety scores by comparison to the control group.

If: A significantly greater decrease in mean POMS Depression-Dejection scores by comparison to the control group.

Ig: A significantly greater decrease in mean POMS Anger-Hostility scores by comparison to the control group.

Ih: A significantly greater increase in mean POMS Vigor-Activity scores by comparison to the control group.

Ii: A significantly greater decrease in mean POMS Fatigue-Inertia scores by comparison to the control group.

Ij: A significantly greater decrease in mean POMS Confusion-Bewilderment scores by comparison to the control group.

Hypothesis II

There will be a significant negative correlation between HardiAttitudes scores on the PVS-III-R and plasma IL-6 levels at baseline and 8 weeks in both groups; there will be a significant positive correlation between scores on the CES-D and plasma IL-6 levels at baseline and 8 weeks in both groups; there will be a significant positive correlation between scores on the TMD of the POMS and plasma IL-6 levels at baseline and 8 weeks in both groups.

Hypothesis III

HardiAttitudes scores on the PVS-III-R will be the single greatest predictor of IL-6 values at baseline and 8-weeks compared to scores on the TMD of the POMS and scores on the CES-D in both control and CBSM groups.

CHAPTER 3

METHODS

The primary purposes of this study were twofold. First, to demonstrate that a CBSM intervention based on the model developed by Lazarus and Folkman (1984) is better than no treatment in reducing Alzheimers dementia and related dementia (ADRD) caregiver stress, as measured by mean scores on the Center for Epidemiologic Studies-Depression (CES-D) and the Total Mood Disturbance (TMD) of the Profile of Mood States (POMS), and in enhancing caregiver immune function, as measured by plasma IL-6 levels. Second, to examine the relationship between the construct of hardiness, as measured by mean scores on the Personal Views Survey-III-Revised (PVS-III-R), and plasma IL-6 levels in ADRD caregivers.

Participants

Participants screened for potential inclusion into this study (N =31) were all familial caregivers (Female 93.5%, Male 6.5%) of ADRD patients and between 49 and 77 years of age ($M= 63.35$; $SD=8.59$). They were recruited over an 11-month span from a major Southwestern (SW; N =12) metropolitan area and a medium-sized Midwestern (MW; N =19) metropolitan area. Of the initial 31 participants screened, five did not meet study

inclusion criteria and two qualified but elected not to participate due to caregiving demands. One participant completed all baseline psychosocial measures, was randomized to the control condition, then dropped out of the study citing conflicts with work schedules. Another participant was randomized to the experimental group, completed all study psychosocial measures, and due to experimenter error the 8-week data were inadvertently destroyed. Inasmuch as there was only one drop out in the current study and that participant was in the no-treatment control group, no intent-to-treat analysis (Fisher, Dixon, Herson, Frankowski, Hearron, & Peace, 1990) was applied to the final data set used for statistical analysis. The remaining twenty-two participants completed all baseline and 8-week measures.

In the MW location, blood samples were drawn at one central location; the lab at a major university health center. The head phlebotomist drew all samples; all samples were handled according to experimental protocol and accounted for.

In the SW location, blood samples were drawn at a local laboratory with multiple locations so participants could choose a geographically convenient location. Initially, the added convenience of a local laboratory was well-received by participants; however, this arrangement led to poor communication between the experimenter, lab management, and the various labs, as well as logistical difficulties, ultimately leading to the loss of four participants' plasma samples. It should be noted that data lost due to laboratory assay issues is not uncommon in biomarker studies (von Kanel, Dimsdale, Mills, Ancoli-Israel, Patterson, Mausbach, et al., 2006). Accordingly, the participant sample that was subjected to final statistical analysis consisted of 18 participants, eight in the no-treatment

control group and ten in the CBSM experimental group, all of whom had complete data for each dependent variable of interest in the research.

The Descriptive statistics for the demographic variables for these 18 participants are shown by location (Southwest or Midwest) and by group type (Control and CBSM) in Table 2. It should be noted that no significant differences were obtained between groups or between locations on the demographic variables shown in the tables.

The demographics of the total sample ($N=18$) were: caregiver (CG) mean age 61.89 ($SD=8.55$), care recipient (CR) mean age 73.22 ($SD=11.82$); racial composition was 94.5 % Caucasian, 5.5 % African-American; and gender was 100% female. Relationally, most caregivers were spouses (83.5%), with daughters (16.5 %) also represented. Socio-economic status as determined by mean yearly income was in the range of \$30,000-39,000, and all participants had at least a high school diploma (mean years of education = 14.39; $SD=1.54$). No significant differences between participants by location or group type were found on any of the above listed variables.

Additional variables commonly examined in caregiving and biomarker research, and of interest in this study were: duration (months) of the caregiving experience ($M=59.89$; $SD=41.64$ Median= 42.0); daily hours spent in caregiving ($M=9.33$; $SD=4.06$); and degree of CR impairment as indicated by mean number of ADLs ($M=3.94$; $SD=2.90$) and IADLs ($M=6.17$; $SD=1.25$) endorsed by the caregiver. Additionally, the caregivers own perception of their current physical health was assessed with a self-report measure using a 5-pt. Likert-scale (1="poor", 3= "good", 5="excellent"). Most CGs reported their current physical health as "good" ($M=3.33$; $SD=.84$). Using one-way ANOVA ($F(1,16)$), no significant differences among participants

by location or group type were found on any of additional variables examined. Table 2 summarizes this demographic information for the study sample.

Inclusion Criteria

All participants that were entered into the study lived with and provided care for a relative, significant other, or personal friend for a minimum of four hours per day for at least the past six months. Additionally, participants were conversant in English and had at least a 10th-grade education.

Participants committed to remain in their respective site area for two months, had a telephone, and reliable transportation. The care recipients had a medical diagnosis of probable ADRD or a Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) score of 24 or lower, indicative of at least moderate cognitive impairment. In order to ensure that caregivers were involved in tasks and responsibilities that could be burdensome on a daily basis, care recipients had a minimum of two dependencies in their instrumental activities of daily living (IADLs; Lawton & Brody, 1969), or one limitation in basic activities of daily living (ADLs).

Exclusion Criteria

Exclusion criteria for this study were based on previous research with II-6 and dementia caregivers (Kiecolt-Glaser, et al., 2003; Lutgendorf, et al., 1999). Participants were excluded from the study for the following factors known to influence immune function: use of systemic corticosteroids within the past three months; history of chemotherapy or radiation in the past 5 years; active diseases that could affect immune function, such as cancer, rheumatoid arthritis, AIDS, lupus and multiple sclerosis;

infectious disease such as a cold or flu within two weeks of study entry; serious illness requiring hospitalization.

Table 2
Means and Standard deviations for demographic variables pertaining to location and group type

Variable	Location		Group type	
	Southwest (n = 4)	Midwest (n = 14)	Control (n=8)	CBSM (n=10)
CG Age				
Mean (SD)	60.0 (6.73)	62.43 (9.15)	59.50 (9.49)	63.80 (7.67)
CR Age				
Mean (SD)	72.75 (3.78)	73.36(13.40)	76.38(15.82)	70.70 (7.30)
Race				
Caucasian	3 (75%)	14 (100%)	7 (87.5%)	10 (100%)
African-American	1 (25%)		1 (12.5%)	
CR Impairment				
ADL				
Mean (SD)	4.25 (1.71)	3.86 (3.21)	4.25(3.54)	3.70 (2.45)
IADL				
Mean (SD)	6.50 (.58)	6.07 (1.39)	6.25 (1.17)	6.10 (1.37)
Education				
Mean (SD)	15.25 (.96)	14.14 (1.61)	14.63(1.60)	14.20 (1.55)
Months CG				
Mean (SD)	88.0 (24.66)	51.86(42.60)	56.25 (42.18)	62.80 (43.25)
Hours/day in CG				
Mean (SD)	7.00 (1.41)	10.0 (4.35)	9.25 (5.10)	9.40 (3.31)
CG Health	3.00 (.82)	3.43 (.85)	3.50 (1.07)	3.20 (.63)
Poor	0	0	0	0
Fair	1	1	1	1
Good	2	8	4	6
Very Good	1	3	1	3
Excellent	0	2	2	0
Income				
(in thousands of U.S. \$)	40-49	30-39	30-39	40-49

Note: Gender is not listed as a variable as all study participants were female.

or bedrest of more than 7 days within three months of study entry; currently taking any immunosuppressive medication; an organ transplant within the past year; currently consuming more than four ounces of alcohol per day; or currently in psychotherapy.

To protect confidentiality, identifying information was removed from the testing instruments, and coded with an identifying number. All study data were kept in locked filing cabinets in a secure room, with identifying information separated from study data.

Setting

The specific site (s) for initial interviews, all study tests and measurements, and experimental groups varied by location. For participants randomized to the experimental condition in the SW location, initial interviews, study instrument administration, and the experimental group took place at a local assisted living facility. For control group participants, the initial interview and study instrument administration took place in their homes. For participants randomized to the experimental condition in the MW location, initial interviews, study instrument administration, and the experimental group took place at a local rehabilitation hospital with a dementia daycare unit. As with control group participants in the SW location, the initial interview and study instrument administration took place in their homes. In both locations, the facility that the CBSM groups took place in provided gratis daycare services for the group participants' ADRD family member.

Experimental design

This study was a multi-site experimental design, with participants assigned in alternating blocks of four to either an experimental group, or a no-treatment control group (alternate blocked assignment). There were repeated measures collected at baseline (pre-intervention) and at 8 weeks post-baseline (post-intervention). This study followed a

randomized controlled clinical trials design, and evaluated psychological and immune outcome measures of a cognitive-behavioral intervention (CBSM) compared to a no-treatment control group.

Measures

The initial baseline interview contained measures utilized in the REACH study, which were duplicated in this study for demographic and inclusion/exclusion purposes and not repeated at the 8-week measurement. These included a: demographics questionnaire and measures of Activities of Daily Living (ADLs; Katz, Ford, Moskowitz, Jackson, & Jaffe, 1973) and Instrumental Activities of Daily Living (IADLs; Lawton & Brody, 1969). The following measures were used as dependent variables and were employed at baseline and 8-weeks: Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977; REACH, 1997), Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981), the Personal Views Survey-III-R (PVS-III-R; Maadi, 1999), and plasma levels of Interleukin-6.

Dependent Measures

Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977)

The CES-D is the most frequently used standardized self-report scale in caregiving studies (Garand, 2000; Schulz, et al., 1990). It is a 20-item instrument with scores that can range from zero to 60. Scores at or above the CES-D cutoff of 16 indicating a risk for clinical depression (Radloff, 1977). Typical population scores are 7.4 to 9.4 (Blazer, 1994; Radloff, 1977). Scores of elderly dementia caregivers on the CES-D are at or above the CES-D cutoff (16) in an estimated 33-39% of all cases (Schulz, O'Brien, Bookwala,

& Fleissner, 1995). Epidemiological research indicates that in the general community-dwelling elderly, about 15% of the population is at risk for scoring above the cut-off score (Blazer, 1994).

The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981).

The POMS is a 65-item factor analytically derived inventory that uses a 5-point Likert –type adjective rating scale ranging from “Not at all” (0) to “Extremely” (4). Participants are asked to rate each item based on how they were feeling in the week and day they completed the inventory. The POMS measures six mood states: Depression-Dejection (DD), Tension-Anxiety (TA), Anger-Hostility (AH), Vigor-Activity (VA), Fatigue-Inertia (FI), and Confusion-Bewilderment (CB). A Total Mood Disturbance (TMD or Total Mood) score is derived by totaling the scores across all six mood states, with Vigor being weighed negatively. Factor structures similar to the original standardized samples were found in studies using older subjects (Kaye, 1988). Internal consistency for the six scales ranges from 0.84 to 0.95 (McNair, et al., 1971).

The POMS has been widely used, is reliable and valid for persons with a minimum of a sixth grade education, correlates highly with other scales used to measure mood states, and has been shown to be sensitive to experimental manipulations in non-psychiatric populations (Garand, 2000). Peterson & Headen (1984) have reported construct validity with high correlations between the POMS and other scales measuring various types of emotional states. A 1999 study (Buckwalter, Gerdner, Kohout, Hall, Kelly, Richards, & Sime) with caregivers demonstrated test taking time for the POMS to be approximately 15 minutes for the caregivers, and that scores on the POMS provided an understanding of

the level of psychological discomfort experienced by the caregivers (Buckwalter, et al., 1999).

The Personal Views Survey-III-Revised (PVSIII-R; Maddi & Khoshaba, 1999)

The PVSIII-R is an 18-item instrument that uses a 4 point Likert-type scale with responses ranging from “Not at all true” (0) to “Very true”(3). Factor analyses (Bartone, Ursano, Wright, & Ingraham, 1989) have yielded three inter-correlated factors identifiable as Commitment, Control, and Challenge. Thus, the PVS-III-R yields a total hardiness score (HardiAttitudes), with scale scores for Commitment, Control, and Challenge (Bartone, et al.,1989; Maddi & Khosahba, 1994). Alpha coefficients estimating internal consistency and reliability were .55-.75 (commitment), .64-.84 (control), .61-.88 (challenge), and .74 for total hardiness (Maddi, Harvey, Khoshaba, Lu, Persico, & Brow, 2004). No significant correlations between total hardiness or Control, Challenge, and Commitment with age, gender, or race have been noted (Maddi, et al., 2004).

The PVSIII-R is derived from the 18 best items from the PVSIII, which in turn consists of the 30 best items of the PVSII. The PVSII is a 50-item rating scale, and is a third-generation measure of hardiness with adequate reliability. Internal consistency scores range from .70-.75 for commitment, .61-.84 for control, and .80-.88 for challenge (Maddi, 1997). In addition, the PVSII has a coefficient alpha of .84 for the total Hardiness score (Maddi, Khoshaba,Persico, Lu, Harvey, &Bleeker, 2002) and 6-month stability estimates around .60. (Maddi, Wadhwa, & Haier, 1996).

Interleukin-6

IL-6 has been shown to be a reliable and valid biological indicator of the presence of chronic stress and is associated with adverse physiological events (H. J. Cohen, Pieper, Harris, Rao, & Currie, 1997; Hammerman, 1999; Taaffe, Harris, Ferrucci, Rowe, & Seeman, 2000).

Regarding IL-6 Norms: according to R&D Systems (ELISA manual), the mean IL-6 value in human subjects tested (N = 52) was 1.77pg/ml, and the range was 0.447-9.96 pg/ml. Epidemiological studies of individuals age 65 and older have found the following values: highest quartile > 3.19 pg/ml (Mean = 2.08 pg/ml., lowest quartile; < 1.46 pg/ml.; Harris, Ferrucci, Tracy, Corti, Wacholder, Ettinger, Heimovitz, et al., 1999; Reuben, Ferrucci, Wallace, Tracy, Corti, Heimovitz, & Harris, 2000). As one illustration of risk, participants in the upper quartile had a 200% greater risk of death when compared to the lowest quartile (Harris, et al., 1999).

Procedures

As this was a multi-site study, Institutional Review Board (IRB) approval was obtained from the Office for the Protection of Human Subjects (OPRS) at the presiding universities in both locations. After IRB approval was obtained, participants were recruited from their respective Southwest (SW) or Midwest (MW) locations. Recruitment strategies consisted of mass media and electronic advertising; mass distribution of flyers; liaisons with local aging agencies; and promotional talks given to support groups, area agencies, and professionals.

In the SW location, after review by their own IRB, the local Alzheimers Association agreed to refer callers on their caregiver assistance line to the study. They also distributed flyers at a local caregivers conference, and included a flyer in their monthly newsletters. A local assisted living facility agreed to provide daycare services for group participants and refer potential participants. Approximately 1500 flyers with brief study descriptions were distributed to local assisted living facilities, neuropsychologists' offices, and the local school of medicine neurology clinic. Another 1500 flyers were distributed at the main libraries in the area, as well as at all the Senior Centers.

In the MW location, after review by their own IRB, a local neurological rehabilitation hospital that had a dementia unit agreed to provide daycare services for group participants and refer potential participants. Outreach efforts to the local Alzheimer Association and Agency on Aging resulted in approximately 2500 flyers with brief study descriptions being sent to caregivers, attached to the monthly newsletter, and an article being published detailing the study. The local public radio station aired public service announcements, and the local National Public Radio (NPR) affiliate conducted an interview and placed information on their web page. Additionally, the local newspaper with a circulation of over 175,000 did an interview that resulted in a feature article being written. They also hosted information on their web page. Lastly, multiple speaking engagements at local support groups, assisted living facilities, aging agencies, and Alzheimer Associations that attract caregivers took place.

Potential participants responded to a phone number belonging to the principal investigator (PI). Typically, the caller had several questions about the study. Once those were answered, the PI requested permission to conduct a brief screening interview. No

caller refused the request; a waiver of informed consent was then obtained from the interviewee during the initial section of the phone interview and prior to proceeding with any study-related questions. A documentation of waiver of informed consent was filed and approved by IRBs in both locations. If the participants meet inclusion criteria and agreed to participate in the study, they were then randomly assigned to either the control group or the CBSM group, in an alternate randomization block design. An appointment was then scheduled for the first face-to-face interview, at the beginning of which written informed consent was obtained. However, due to the timeline of immunological sample analysis, no particular group started baseline measurements, which started the study clock ticking, until at least four participants had been assigned to that group and completed their face-to-face interview. All participant blood draws took place within 72 hours after that interview.

Both groups completed identical measures (CES-D, POMS, and PVSIII-R) at study entry and 8 weeks post-study entry (control group) or immediately upon post-intervention completion (8 weeks post-treatment initiation; experimental group).

Both groups had blood samples taken at both measurement points within 72 hours after each study measure administration. All blood draws took place between 7:30 A.M. and 11 A.M. to minimize potential diurnal variation. All blood draws were conducted by licensed phlebotomists or registered nurses (RNs). Participants underwent a venipuncture of the forearm withdrawing 10 ml. of blood using a 21-gauge Precision glide needle into a heparinized (anti-coagulant) tube. Whole blood samples were then centrifuged immediately at 2500 RPM for 10 minutes at room temperature. The plasma was then removed, labeled with the participant's identification code and date, frozen at -40 ° C, and

stored in the laboratory freezer until analysis. Following established research recommendations, all samples were thawed in batches and assayed by the same laboratory technician blind to the hypotheses of the study using a Quantikine High Sensitivity Human IL-6 Immunoassay Kit (ELISA) per kit instructions.

Control group members received a five-minute appointment-reminder phone call from a research assistant two weeks and one week prior to their 8-week appointment. The phone calls followed a standardized brief protocol and were intended to maintain contact and reduce attrition. Experimental group members received verbal reminders by the group leader in the group session one week prior to the schedule sample date. During the course of the study, only one participant discontinued participation in the study; that individual left the study immediately after baseline measures were obtained citing conflicts with her work schedule.

In the experimental groups, each group meeting session lasted approximately 90 minutes, for a total of eight sessions over the course of eight consecutive weeks. Group size was limited to a maximum of eight and a minimum of four participants.

The experimental group received a Cognitive-Behavioral Stress Management (CBSM) intervention designed to teach appraisal of problems as a challenge, to increase coping skills through the generation of options, to teach a problem-solving approach, and to enhance the individual caregiver's sense of competency, control, and choice. The CBSM group in the SW location was led by a single graduate-level, trained research assistant following a manualized protocol. The PI led the MW location CBSM group following the same manualized protocol. All CBSM participants received a participant's manual.

Individual participants were not paid for participation in the study, but will receive information on their test results post-study completion.

Experimental Intervention Details

Cognitive-Behavioral Stress Management (CBSM) intervention

There were a total of eight weekly meetings of the group receiving the CBSM intervention, each lasting approximately 90 minutes. The intervention followed the theoretical framework of Lazarus and Folkman (1984), and employed the Coping with Caregiving manual (Stanford University School of Medicine, 2000). Each meeting consisted of Homework review (in Class I introductions took the place of homework review), one or two psychoeducational components, an in-class exercise(s), review of material covered, and a homework assignment. In the final session, Class VIII reviewed the CBSM intervention material presented during the course of the intervention, and Certificates of Completion were presented.

Class I consisted of going over the goals of class, a psychoeducational overview of Dementia, understanding caregiver frustration, and discussing the Caregiver Bill of Rights. The Relaxation exercise that was in each class was introduced and conducted, along with the Relaxation ratings scale. Homework assigned was to review the readings pertaining to Class I, which simply summarized the material reviewed in class.

Class II introduced the “ABC” (Actions, Behavior, Consequences) Model to the participants, beginning with Part One: Identifying Unhelpful Thoughts About Caregiving. The concept of appraisal of caregiving challenges was presented in the form of harm/loss, threat or challenge. Appraising caregiving problems as challenge was proposed as a stress-reducing form of appraisal. Participants were assigned homework focusing on the

ABC model, and asked to use the worksheet called “Diary of thoughts”. They were asked to select a particular situation during the week immediately passed that caused them to feel frustrated and angry as a caregiver. Caregivers were instructed to write down all the negative thoughts that have occurred to them as a result of what happened, and be prepared to share those thoughts in Class III. The Relaxation exercise was conducted, and participants rated the quality of their relaxation prior to and immediately following the exercise.

Class III reviewed homework from the previous class, and participants were asked to discuss a problem-solving approach to an incident that occurred to a member of the group in the previous week. The group also covered the “ABC” Model Part Two: negative thoughts, danger signals, and stop signs {ABC-Stop}. For homework, participants were asked to complete the ABC (STOP): Diary of Thoughts worksheet. The Relaxation exercise was conducted, and participants rated the quality of their relaxation prior to and immediately following the exercise.

In Class IV the focus was on achieving adaptive thoughts and behaviors. Homework was reviewed, and the concept of appraisal as challenge along with problem-solving approaches was discussed and lead into the homework assignment. The homework focused on the “ABC” Model Part Three: Changing Unhelpful Thoughts into Adaptive Thoughts and Linking Them to Behaviors (Actions) {ABC-Stop-D}. The class moved from action-behavior-consequences-STOP- to Different (behaviors, choices, means of coping, problem solving, etc.). The Relaxation exercise was conducted, and participants rated the quality of their relaxation prior to and immediately following the exercise. Homework was assigned focusing on the ABC-STOP-D exercise.

Class V focused on viewing behavior as communication, understanding various types of communication (Passive, Assertive, and Aggressive) and Practice Exercises.

Participants discussed the choices of the types of communication they use as an aspect of control of their environment. The Relaxation exercise was conducted, and participants rated the quality of their relaxation prior to and immediately following the exercise.

Homework consisted of continuing with the Diary of Thoughts and the Assertiveness Practice Sheet.

In Class VI, the focus was on practicing how to be more assertive in caregiving situations and with family members, and extending the issues of choice, control and communication to caregiving situations with family members. The group also had an introduction to “Pleasant Events and Mood Monitoring; Identifying Potential Pleasant Events and Activities” that affect everyday mood and learning to monitor them daily in order to improve feelings of well-being. The Relaxation exercise was conducted, and participants rated the quality of their relaxation prior to and immediately following the exercise. Homework continued with Assertiveness Practice, and identifying pleasant events that had a positive effect on caregiver mood.

Class VII covered the areas of understanding and overcoming personal barriers to increasing everyday pleasant events and activities, and practicing how to increase everyday pleasant events and activities for the caregiver as well as the care recipient. The class discussed the effect of choices on caregiver mood, and identified the control that caregivers have over many of their choices. The Relaxation exercise was conducted, and participants rated the quality of their relaxation prior to and immediately following the

exercise. For homework, participants completed a daily mood rating form, and a pleasant events tracking form.

Class VIII was the final session and consisted of a Review of Major Skills Taught, such as: 1. Tracking unhelpful thoughts related to caregiving; 2. Challenging unhelpful thinking patterns and developing more adaptive ones; 3. Seeing how thoughts influence behavior and everyday actions; 4. Reframing the appraisal of stressful events as manageable challenges, and manageable challenges as solvable problems; 5. Learning to be more assertive regarding caregiving; 6. Learning to identify pleasant events and activities that can be done on a regular basis; 7. Tracking mood and understanding how thoughts and behaviors influence and control mood; 8. Identifying pleasant activities to be shared with my relative. The class then addressed how to use these skills in the future. The last Relaxation exercise was conducted, and participants rated the quality of their relaxation prior to and immediately following the exercise. This was followed by a discussion of imminent termination of the class, closing remarks, and awarding certificates of completion.

Group leaders audiotaped all group sessions for subsequent reliability and validity evaluations of treatment protocol adherence.

Research assistants

The study required two clinical psychology graduate research assistants in addition to the PI for the purposes of administering study measures, leading the intervention groups and running the day-to-day activities of the study. It also required two undergraduate research assistants for data check and entry purposes. All graduate and undergraduate research assistants were identified to the IRB and had CITI certification.

The graduate research assistants were oriented to study procedures and protocol, and trained in the delivery of the CBSM intervention by the PI. The undergraduate assistants were psychology majors with high academic standing. They were trained in data entry procedures for SPSS, oriented to study protocols, and blind to treatment condition.

Treatment Integrity

Several strategies were employed to ensure the integrity of treatment (Yeaton & Sechrest, 1981): (1) Group leaders used a detailed script specifically designed for each session, indicating the materials needed, tasks to be completed, the order in which those tasks needed to be completed, and homework assignments for the participants; (2) Self-monitoring by the group leader of treatment protocol adherence using a prompting checklist; (3) all group sessions were audiotaped and the tapes used for treatment adherence reliability estimation by a rater blind to the study hypotheses; (4) ongoing supervision of the research assistants involving task adherence, problem solving, and corrective feedback by the PI as needed.

Prompting lists were used to obtain reliability and validity estimates. Specifically, after class completion, the therapists indicated whether or not they had implemented each therapy task by marking the appropriate box on the prompting list. Due to ethical issues, logistical difficulties arising from the multi-site design, and HIPAA restrictions involving transportation by mail of sensitive study material, the PI functioned as a rater. This involved listening to 10% of the group audiotapes chosen at random and then using the same prompting list to evaluate whether the group leader had implemented the specified tasks. The reliability estimate was based on both the therapist and rater lists, and was calculated by dividing the number of tasks both the therapist and rater indicated as

completed by the number of tasks possible. The validity estimate was based only upon the therapist list and was calculated by dividing the number of tasks completed by the total number of possible tasks.

Data Entry, Outliers, and Intent-to-treat

Two person data entry teams entered raw data into SPSS (v 13) to ensure accuracy of data entry. Descriptive statistics for each of the variables were calculated and examined in order to detect out-of range values, evaluate the presence of outliers, and inspect the distribution of each of the major variables. Where out-of-range values were present, the raw data were examined to ensure that the outlier was not a result of data entry error. If outliers were still present (± 2.5 SD), subject characteristics were evaluated to determine if the subject was a representative member of the study participant group.

One participant met the a priori definition and was classified as a potential outlier. However, upon close examination of the demographic variables, this participant was determined to be a representative member of the study participant group. Using one-way ANOVA, baseline dependent variables were examined with ($F(1,16)$) and without ($F(1,15)$) the outlier participant data included and no significant differences between groups on the dependent variables were found. Thus, the outlier designation did not apply in this case, and the participant's data were included.

CHAPTER 4

RESULTS

The overarching purposes of this study were twofold. The first purpose was to determine whether a CBSM intervention based on the model developed by Lazarus and Folkman (1984) is better than no treatment in reducing ADRD caregiver stress, as measured by mean scores on the CES-D and the TMD of the POMS, and in enhancing caregiver immune function, as measured by plasma IL-6 levels. The second purpose was to examine the relationship between the construct of hardiness, as measured by mean scores on the PVS-III-R, and plasma IL-6 levels in ADRD caregivers.

So as to address these purposes empirically, a series of three major hypotheses were put forward and will serve to structure the subsequent consideration of the results obtained.

A summary of the group means and standard deviations for the major dependent variables of Center for Epidemiological Studies for Depression scale (CES-D), the Total Mood Disturbance from the POMS, the HardiAttitudes scores from the PVSIII-R, and plasma concentrations of IL-6 at baseline and 8-weeks are provided below in Table 3. Group means and standard deviations for the six subscales of the POMS (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, and Fatigue-Inertia) at baseline and 8-weeks are provided below in Table 4.

Table 3. Means and standard deviations for dependent variables at baseline and 8-weeks for the no-treatment control and CBSM treatment groups.

	Control (n=8)		CBSM (n=10)	
	Baseline	8 weeks	Baseline	8 weeks
	M (SD)	M (SD)	M (SD)	M (SD)
CES-D	10.50(6.39)	15.13(11.06)	16.33(7.94)	10.10(5.88)
TMD	33.00(26.33)	29.38(32.33)	49.78(25.26)	24.70(22.94)
HA	37.13(6.81)	36.38(5.68)	37.44(4.22)	39.30(4.37)
IL-6	1.038(.90)	.870(.596)	1.68(2.28)	1.923(.267)

Note: HA= HardiAttitudes; TMD= POMS total mood disturbance; CESD= Center for Epidemiological Studies-Depression; IL-6= Interleukin-6 concentration (pg/ml)

Hypothesis I

The first overall hypothesis was that CBSM would improve the well-being of familial caregivers. Table 3 presents the means and standard deviations for the main dependent variables at baseline and 8 weeks for the no-treatment control and the CBSM treatment groups. As was anticipated from the random assignment of participants to groups, on-way ANOVAS yielded no significant mean differences in the dependent variables at baseline between the control and CBSM groups, $F(1,16)$.

Four one-way, within-subjects repeated measures analyses of variance (rmANOVA) were conducted to evaluate the effects of the CBSM intervention on the well-being of familial caregivers. More specifically, the analysis examined the effects of group (control or CBSM) on caregiver well-being as evidenced by changes from baseline to 8 weeks in the mean values of the dependent variables in this study.

For Hypothesis 1a, the dependent variable was mean CES-D scores and the expectation was that there would be a greater decrease in these scores for the CBSM group than the control group. The main effect for the CES-D scores was not significant.

There was, however, a significant CES-D x group interaction ($F(1,16) = 6.66, p = .020$). Two paired-samples t tests were conducted to follow up this significant interaction. For the control group, differences in mean CES-D scores were not significantly different between baseline and 8-weeks, $t(7) = -1.48, p = .183$. For the CBSM group, differences in mean CES-D scores were significantly different between baseline and 8-weeks, $t(9) = 2.28, p = .049$. Indeed, Table 3 shows that the mean CES-D scores decreased for the CBSM group across the eight weeks while actually trending upward for the control group. These results support a conclusion that the CBSM intervention improved caregiver well-being by producing a significant decrease in subjective symptoms of depression at least as measured by mean scores on the CES-D.

For Hypothesis 1b, the dependent variable was mean TMD of the POMS scores and the prediction was that CBSM would decrease overall mood disturbance as compared to no treatment. This is suggested by Table 3 where a larger decrease from baseline in the mean TMD score is shown at the end of the 8-week treatment than for the control group. A rmANOVA yielded a significant main effect for the TMD scores, $F(1,16) = 6.55, p = .021$. The interaction of TMD x group approached but did not quite achieve significance, $F(1,16) = 4.33, p = .054$.

Two paired-samples t tests were conducted to further explore the significant main effect. For the control group, differences in mean TMD scores were not significantly different between baseline and 8-weeks, $t(7) = .39, p = .711$. For the CBSM group, differences in mean TMD scores were significantly different between baseline and 8-weeks, $t(9) = 3.13, p = .012$. These results broaden the conclusion suggested above for the CES-D scores that the CBSM intervention improved caregiver well-being as

compared to the no-treatment control group, in this case as evidenced by the significant decrease in total mood disturbance for the CBSM group.

Hypothesis 1c was that total hardiness, as reflected in the HardiAttitudes score, would show a greater increase following CBSM treatment than for a no-treatment group. In other words, it was hypothesized that the treatment would enhance caregivers' well-being by increasing their overall hardiness. This hypothesis was not confirmed. There was neither a significant main effect of the HardiAttitude scores, $F(1,16) = 1.59, p = .225$ nor a HardiAttitudes x group interaction, $F(1,16) = 3.22, p = .092$.

For Hypothesis 1d the dependent variable was plasma IL-6 concentrations. It was anticipated that this biological marker of stress would be sensitive to CBSM treatment and show a decrease in comparison to IL-6 control levels reflecting a treatment-induced reduction in stress and corresponding increase in caretaker well-being. However, despite the obtained significant decreases in subjective depression and total mood disturbance, there was no significant main effect of plasma IL-6 concentrations, $F(1,16) = .03, p = .864$ or an IL-6 x group interaction, $F(1,16) = 1.06, p = .319$.

The Total Mood Disturbance score for the POMS that was discussed above is obtained by summing the scores on five of the six mood states measured by the POMS, and subtracting the sixth scale from that total. The positively weighted mood scales are Depression-Dejection, Tension-Anxiety, Anger-Hostility, Fatigue-Inertia, and Confusion-Bewilderment. The negatively weighted scale is Vigor-Activity. Research hypotheses 1e-1j stipulated, respectively, that CBSM would produce a greater change in these mood scales than the no-treatment control in the direction of caregiver well-being. This would

involve a decrease in each subscale except for Vigor-Activity, which it was hypothesized would show an increase.

Table 4. Means and standard deviations for POMS subscales at baseline and 8-weeks for the no-treatment and CBSM treatment groups.

	Control (<i>n</i> =8)		CBSM (<i>n</i> =10)	
	Baseline	8 weeks	Baseline	8 weeks
	M (SD)	M (SD)	M (SD)	M (SD)
DD	10.38(5.83)	9.88(9.78)	21.00(13.29)	10.00(6.73)
TA	9.63(4.84)	8.13(6.88)	13.30(7.09)	8.70(3.37)
AH	8.88(9.46)	9.63(10.31)	15.90(10.08)	7.60(4.79)
FI	11.50(6.00)	9.38(8.05)	13.40(7.52)	9.40(5.25)
CB	7.88(2.75)	7.13(2.80)	9.70(4.37)	7.90(2.60)
VA	15.25(3.92)	14.75(5.26)	13.40(5.46)	18.90(5.90)

Note: DD= POMS Depression-Dejection; TA=POMS Tension-Anxiety; AH=POMS Anger-Hostility; FI= POMS Fatigue-Inertia; CB= POMS Confusion-Bewilderment; VA= POMS Vigor-Activity

Table 4 above presents the mean and standard deviation for each of the six mood states as obtained at baseline and after eight weeks in the no-treatment control group and CBSM treatment group. As can be seen from Table 4, each of the mood states in the CBSM group showed a change in mean scores in the predicted direction from baseline to eight weeks. However, rmANOVAs run separately for each hypothesis 1e-1j yielded significance only for Hypothesis 1f, namely for the Depression-Dejection (DD) mood scale. Indeed, both the main effect of DD, $F(1,16) = 6.33, p = .023$, and the DD x group interaction, $F(1,16) = 5.28, p = .035$ were significant. Two paired-samples *t* tests were conducted to follow up the significant interaction. For the control group, differences in mean Depression-Dejection scores were not significantly different between baseline and

8-weeks, $t(7) = .19, p = .855$. For the CBSM group, differences in mean Depression-Dejection scores were significantly different between baseline and 8-weeks, $t(9) = 3.15, p = .012$

Additionally, on Hypothesis 1h a trend towards significance, $F(1,16) = 4.40, p = .052$ was noted for the interaction of Vigor-Activity x group.

In summary, taken as a whole, the results obtained under Hypothesis 1 suggest that an eight-week CBSM intervention improves caregiver well-being as compared to a control group. This was evidenced by a significant decrease in subjective symptoms of depression as measured by the CES-D and Depression-Dejection mood scale of the POMS, and an overall improvement in mood as measured by the TMD of the POMS. On the other hand, it is noted that corresponding significant differences were not found for a measure of hardiness or for the biological marker of stress measured in this research, namely IL-6.

Hypothesis II

In order to investigate the hypothesis that correlations between IL-6, HardiAttitudes, CES-D, and the TMD of the POMS would be significant, Pearson product moment correlation coefficients were computed among the four dependent variables at baseline and separately at eight weeks. Using the Bonferroni approach to control for Type I error across the 6 correlations at each time, a p-value of less than .008 ($.05/6 = .008$) was required for significance. It was hypothesized that each of the dependent variables, IL-6, CES-D, and TMD would be positively correlated with one another while each of these would, in turn, be negatively correlated with HardiAttitudes.

The results of the correlational analysis for baseline are presented in Table 5 and results of the correlational analysis for eight weeks are presented in Table 6 below. As can be seen in these tables several, but by no means all of the correlations were in the predicted direction. Moreover, none of the correlations involving HardiAttitudes or IL-6 were significant at baseline or at eight weeks. Indeed, the only consistent significant correlations obtained were the positive correlations between CES-D and TMD at baseline ($p < .001$) and at eight weeks ($p < .001$).

Table 5. Correlations among dependent variables at baseline.

	HAT-T1	TMD-T1	CESD-T1	Con-T1
HAT-T1	1			
TMD-T1	-.599	1		
CESD-T1	-.573	.855(*)	1	
IL-6-T1	-.003	.253	-.046	1

*Significant at the 0.001 level (2-tailed)

Note for Table 5: HAT-T1= HardiAttitudes baseline; TMD-T1= POMS total mood disturbance baseline; CESD-T1=Center for Epidemiological Studies-Depression- baseline; IL-6-T1= IL-6 concentration baseline

Hypotheses III

In order to investigate the hypothesis that HardiAttitude scores would be the single greatest predictor of IL-6 plasma concentrations for both groups at baseline and eight weeks compared to the TMD of the POMS and the CES-D, two multiple regression analyses were conducted. One analysis included Hardiattitude, CES-D, and TMD of the POMS scores as predictors of IL-6 concentrations at baseline, while the second analysis

included Hardiattitude, CES-D, and TMD of the POMS scores as predictors of IL-6 concentrations at 8-weeks.

Table 6.
Correlations among dependent variables at eight weeks.

	HAT-T2	TMD-T2	CESD-T2	Con-T2
HAT-2	1			
TMD-T2	-.583	1		
CESD-T2	-.585	.744(*)	1	
IL-6-T2	.063	-.166	-.019	1

* Significant at the 0.001 level (2-tailed)

Note for table 6: HAT-T2= HardiAttitudes 8-weeks; IL-6-T2= IL-6 concentration 8-weeks; TMD-T2= POMS total mood disturbance 8-weeks; CESD-T2=Center for Epidemiological Studies-Depression- 8-weeks

For the first multiple regression analysis, the linear combination of the predictors was not significantly related to plasma concentrations of IL-6, $F(3,14) = 1.51, p = .257$. The sample multiple correlation coefficient (R) was .49, indicating that approximately 24% of the variance (R^2) could be accounted for by the linear combination of the predictors.

None of the three bivariate correlations was statistically significant. Contrary to prediction, HardiAttitudes was the least significant of the three predictors, accounting for less than .001% ($-.02^2 = .0004$) of the variance in plasma IL-6 concentrations at baseline. Unexpectedly, CES-D accounted for the greatest proportion of the variance in plasma IL-6 concentrations, 2% ($-.14^2 = .02$). The TMD of the POMS accounted for 1.7 % ($.13^2 = .017$).

For the second multiple regression analysis on the eight week data, the linear combination of the predictors was not significantly related to plasma concentrations of IL-6, $F(3,14) = 1.08, p = .390$. The sample multiple correlation coefficient (R) was .43,

indicating that approximately 19% of the variance (R^2) could be accounted for by the linear combination of the predictors. Similar to the first multiple regression analysis, none of the three bivariate correlations was statistically significant. Again contrary to prediction, HardiAttitudes was the least significant of the three predictors, accounting for 5% ($-.22^2 = .05$) of the variance in plasma IL-6 concentrations at eight weeks. Unlike the first multiple regression, in the second multiple regression the TMD of the POMS accounted for the greatest proportion of the variance in plasma IL-6 concentrations, 18% ($-.43^2 = .18$). The CES-D accounted for 7 % ($-.27^2 = .07$).

Treatment Integrity

Validity estimates for the study were obtained by dividing the number of tasks checked as completed by the therapist leading the experimental group by the total number of assigned tasks for the eight sessions of the CBSM group. In both the SW and MW locations, the therapists recorded 100% compliance with task assignment. In the SW location, tape recordings of the group sessions were not available due to therapist error, so reliability estimates could not be obtained. In the MW location, listening to a random selection of taped sessions resulted in 99% interrater agreement. However, it must be noted that the therapist that led the CBSM in the MW location also functioned as the rater.

Group Attendance

Participant attendance at group sessions was also tracked and evaluated. Of the total 80 sessions possible (10 CBSM group participants x 8 sessions), participants missed 4 sessions, resulting in a total attendance of 95%. No participant missed more than one

session. All participants were provided with a CBSM group manual, and were instructed to cover the missed material prior to the next group. In each case of a missed group session, the group leader contacted the participant prior to the next group to answer any questions about the material the participant missed and provide the participant with support and any relevant updates.

CHAPTER 5

DISCUSSION

The participants in this study were Alzheimer's disease and related dementia (ADRD) familial caregivers. They represent a portion of society needing assistance and that is growing both in sheer number and overall percentage of the population. Caregivers dealing with the symptoms of a gradual, progressive, irreversible neurodegenerative disease such as Alzheimer's face numerous emotional, psychological, social, and financial demands that classify ADRD caregiving as a chronic stressor. In addition, familial caregivers are often elderly themselves and are at an increased risk for injury and illness. They face an exacerbation of already declining immune system function due to chronic stress.

This study attempted to enhance immune system functioning and reduce subjective stress levels in the familial caregivers of Alzheimer's disease and related dementia (ADRD) patients. In order to accomplish this objective, a controlled comparison between a cognitively based stress management intervention (CBSM) and a no-treatment control group was conducted. Drawing on the work of Lazarus and Folkman (1984), the CBSM intervention emphasized giving caregiver's psychological tools that would improve their sense of control and engender predictability in their current situation. Thus, this study attempted to increase the ability to cope with the chronic stress of caregiving in familial ADRD caregivers by employing a cognitive-behavioral intervention designed specifically

for that purpose and population.

This study also attempted to make a contribution to the existing body of knowledge in the field of psychoneuroimmunology (PNI) by addressing the complicated inter-relationship between psychological stress and immune system functioning. In this context, it was predicted that the character trait of personal hardiness would diminish the impact of chronic stress on immune system function.

Several years ago, the Advisory Panel on Alzheimer's Disease (1993) recommended that current research emphasize services that reduce the burden of care for familial ADRD caregivers and focus on the implementation and evaluation of interventions aimed at family caregivers. There followed a tremendous upsurge of research that embraced that mandate and the grant availability that came with it.

In the last few years, there has been a shift in the literature investigating the relationship between chronic stress and immune system function in caregivers. It is now widely recommended that researchers employ biological measures (biomarkers) of chronic stress to detect treatment effects in addition to standardized psychosocial measures. This shift has taken place partly in response to: the mounting evidence about the negative impact chronic stress has on immune system function, particularly in the elderly (Grant, et al, 2002; Robinson-Whelen, Kiecolt-Glaser, & Glaser, 2000); the rapidly and dramatically increasing numbers of elderly taking care of the elderly (U.S. AOA, 1999a; Wisniewski et al., 2003); and the consistent failure of psychosocial measures to demonstrate clinical significance in controlled trials with familial caregivers (Cooke, McNally, Mulligan, Harrison, & Newman, 2001; Kneebone & Martin, 2003; Schulz, O'Brien, Czaja, Ory, Norris, Martire, et al., 2002). In fact, at a recent scientific

conference attended by National Institute of Health (NIH) grant recipients, a leading caregiver researcher associated with the REACH studies was told that there is “essentially no more money for caregiver research unless you’re using biomarkers” (Stevens & Hochalter, personal conversation, 2006).

The present study was designed in response to this shift in focus. To date, there have been few studies published that conducted a controlled intervention trial using a biomarker dependent variable. There have been no studies published that conducted a controlled intervention trial using IL-6 as a dependent measure, as this study did.

There were several reasons for the choice of IL-6 as a dependant variable as was elucidated above. To review briefly, serum levels of IL-6 are known to increase with age; IL-6 has been implicated in the processes of normal aging, age-related conditions, and functional decline; IL-6 production may be stimulated by chronic stress and negative emotions such as depression; and circulating levels of IL-6 have been found to increase at a rate four times greater in familial ADRD caregivers than in matched controls (Kiecolt-Glaser, Dura, et al., 1991; Kiecolt-Glaser, Preacher, et al., 2003; Lutgendorf, et al., 1999).

Hypothesis I

It had been predicted that the cognitive-behavioral stress management (CBSM) group would improve the well-being of the familial caregivers as evidenced by significant changes in the mean scores of the dependent variables in question. Further, that change in mean scores would be in the direction specific to that measure that indicated improvement in well-being; increasing in some measures, and decreasing in others.

Hypothesis Ia

In Hypothesis Ia mean scores on the CES-D were the dependent variable. Of particular note in this study is the change in mean scores of the CES-D at 8-weeks within groups. At baseline, the mean CES-D score for experimental group participants was over the depression cutoff score of 16, while the mean for control group participants was not. Comparatively speaking, scores of elderly dementia caregivers on the CES-D are at or above the CES-D cutoff in an estimated 33-39% of all cases (Schulz, O'Brien, Bookwala, & Fleissner, 1995), with about 15% of the general community-dwelling elderly at risk for scoring above the cut-off score (Blazer, 1994). After the intervention, mean CES-D scores in the experimental group had decreased over 6 points to below the cutoff score, while those in the control group increased somewhat toward the cutoff score. These changes produced a statistically significant interaction. This is important, in part, because significant improvements on a psychosocial measure such as the CES-D are atypical in controlled intervention studies with ADRD caregivers.

However, other studies have reported significant results, such as the REACH study. Gitlin et al. (2003) reported that active interventions were significantly better than control conditions at reducing caregiver burden as measured by scores on the Revised Memory and Behavior Problems Checklist (RMPC) Burden scale. Additionally, at the Miami REACH site, a statistically significant association of group assignment was found for the family therapy and computer technology intervention at the six-month point of the intervention on depression as measured by the CES-D.

Hypothesis Ib

In Hypothesis Ib, the dependent variable was mean TMD of the POMS scores. The TMD of the POMS is derived by totaling the scores across all six POMS subscales (Depression-Dejection (DD), Tension-Anxiety (TA), Anger-Hostility (AH), Vigor-Activity (VA), Fatigue-Inertia (FI), and Confusion-Bewilderment (CB)), with VA being weighted negatively. This research demonstrated a significant difference between baseline and 8-weeks for the CBSM group but not for the control group. This result is congruent with the significant change obtained in the CES-D scores, and not entirely surprising inasmuch as the DD mood scale of the POMS contributes 1/6th to the TMD score. Additional discussion on the DD mood scale and the other five POMS subscales is contained within the sections covering Hypotheses Ie-i.

Hypothesis Ic

HardiAttitudes was the dependent variable in Hypothesis Ic. It was expected that HardiAttitudes would increase significantly in the CBSM treatment group as compared to the no-treatment control group. This expectation was based on the conception of hardiness as a personality disposition, a set of attitudes motivating an individual to respond to stressful circumstances in an adaptive manner (Kobasa, 1979), and that hardiness was a personality disposition responsive to intervention (Maadi, 2006). However, no significant changes were found between groups at the 8-week mark, or within groups between baseline and 8-weeks. These results were somewhat surprising, as one study (Johns, 1998) using an earlier version of the PVS with informal caregivers (N = 30) of HIV+/AIDS patients, found a significant negative relationship between burnout and hardiness scores, albeit a concept not addressed in this study. In another

study that used a different measure of hardiness known as the Family Hardiness Index (FHI; McCubbin, McCubbin, & Thompson, 1991) and employing female familial caregivers as participants (N = 67), Clark (2002) found that hardiness was significantly related to fatigue and depression.

Similar to this study, several previous studies (Jensen, 1996; Johnson, 1994; Nunley, 2002; Sussman, 2003) using earlier iterations of the PVS and employing informal caregivers as participants have generally not obtained significant results, typically finding relationships between measures of depression and hardiness that did not reach the level of significance.

Hypothesis Id

Hypothesis Id used mean scores of the plasma concentrations of IL-6 as the dependent variable. There were no significant differences detected between the control and CBSM groups at the 8-week mark on the biomarker dependent variable, IL-6. While there was a change in the IL-6 plasma concentrations between baseline and 8-weeks for every participant in the study, there were no detectable patterns to that change within or between groups at 8-weeks.

While the lack of significance in plasma concentrations of IL-6 was not predicted, in retrospect it might have been anticipated. The length and scope of the intervention need to be considered; eight weeks may simply be an insufficient time to show change in IL-6 concentrations. Generally speaking, shorter behavioral interventions with a narrow scope have yielded results that have been less impactful and enduring, in both the psychological and immunological arenas than longer-term interventions (Kiecolt-Glaser & Glaser, 1992; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Additionally, the use of longer

follow-up periods may have the advantage of showing changes not seen earlier (Fawzy, Fawzy, Hyun, et al., 1993). Indeed, Cooke et al. note (2001) that caregiver interventions may require a delay before their effects are apparent. Two studies that dealt specifically with ADRD caregivers and IL-6 levels, and noted significant change in those levels, had either a longitudinal and matched non-caregiver control design (Kiecolt-Glaser, Preacher, et al., 2003) or a matched non-caregiver control design (Lutgendorf, Garand, et al., 1999). Additionally, the two types of assays discussed in Chapter 1, enumerative and functional, typically operate within different time frames, with the effects from functional assays taking more time to detect.

Another critical factor to consider is the small sample size. Due to difficulty in recruiting participants and the loss of participant sample due to laboratory/assay error (detailed in a previous section), the study likely may have lacked the power to detect significant changes in all cases where they may have existed. In the case of the IL-6 data, it is not possible to discern whether the 8- week interval between measurement or the resultant small N was responsible for a greater contribution to the lack of significance.

The above listed issues are certainly reasonable possible explanations for the biomarker results obtained. However, one other prominent possibility needs to be considered: Homeostasis.

If an intervention is designed to enhance human immune system functioning (an indication of well-being), it could fail simply due to homeostatic regulation. Along similar lines, it should be noted that enhancement of immune system functioning, absent any disease-, stress-, or age- related decline in the subject population, may in fact be undesirable, as an overactive immune system can lead to autoimmune disease (Kiecolt-

Glaser, McGuire, et al., 2002). The mean self-reported health score for study participants was “good”, with only three of the 24 participants reported their health as “fair”, and the remainder of the 24 reporting their health to be “good”, “very good”, or “excellent”. The possibility of a homeostatic ceiling effect cannot be dismissed. Additionally, there has been discussion in the literature of a self-selecting factor in caregiver studies, in that caregivers volunteering for participation are already among the more successful of ADRD caregivers in coping with stress (Patterson, T.L., & Grant, I. 2003).

Hypotheses Ie-i

Hypotheses Ie-i used mean scores on the six subscales of the POMS as dependent variables. Specifically, on Hypotheses Ie (Tension-Anxiety), Ig (Anger-Hostility), Ih (Vigor-Activity), Ii (Fatigue-Inertia), and Ij (Confusion-Bewilderment), no significant effects of the CBSM intervention were found.

Hypothesis If used mean scores of the Depression-Dejection (DD) subscale as the dependent variable. The results showed a significant difference in mean scores of the DD subscale between baseline and 8-weeks for the CBSM group, but not for the control group. This result is similar to the results seen for the CES-D and the TMD of the POMS, supporting the efficacy of the intervention at increasing caregiver well-being, particularly in the area of depression.

As previously noted, obtaining significant change in a psychosocial measure in caregiver intervention studies is uncommon, but not without precedence. In another caregiver study that used the POMS and a biological marker, Hosaka and Sugiyama (2003) used familial dementia caregivers (N = 20) in a Japanese study that utilized a 5-session structured psychoeducational intervention incorporating relaxation. They found

significant change in the subscales of Depression-Dejection, Anger-Hostility, Fatigue-Inertia, and Confusion-Bewilderment.

By way of overall summary of Hypotheses I, the obtained results do support the idea that the CBSM intervention had a demonstrable significant effect in the predicted direction of improving caregiver well-being for the CBSM group on symptoms of depression, as measured by the CES-D and the DD subscale of the POMS, and general mood state, as measured by the TMD of the POMS.

Hypothesis II

Hypothesis II predicted that correlations between HardiAttitude scores and plasma concentrations of IL-6 would be negative and significant at both baseline and 8-weeks; that there would be significant positive correlations between CES-D scores and plasma concentrations of IL-6 at both baseline and 8-weeks; and that there would be significant positive correlations between TMD of the POMS scores and plasma concentrations of IL-6 at both baseline and 8-weeks.

The results proved contrary to prediction. There were no significant correlations between IL-6 levels and any other dependent measure at either baseline or 8-weeks.

The only significant correlations obtained were between CES-D and the TMD of the POMS at both baseline and 8-weeks. These results further substantiate a relationship between these measures as indicated by the results obtained in Hypothesis I, where significant results were obtained on the CES-D and the DD and the TMD of the POMS.

The lack of a significant correlation between HardiAttitude scores and plasma IL-6 concentrations was somewhat surprising. Previous studies have found a moderating

relationship between hardiness and appraisal of caregiving challenges. DiBartolo et al. (2003) addressed the relationship between hardiness, coping, appraisal, and self-appraised health in spouse caregivers (N = 72) of ADRD patients. Using a different measure than this study, and lacking significance, he did note a moderating relationship. Clark (1996) found a negative relationship between hardiness and psychological distress in a population of familial caregivers. Nunley (2002) found an inverse relationship between depressive symptoms and hardiness using the CES-D and the PVS-III, an earlier version of the PVSIII-R employed in this study.

Hypothesis III

Hypothesis III predicted that Hardiattitude scores would be the single greatest predictor of IL-6 plasma concentrations at both timepoints compared to scores on the TMD of the POMS and scores on the CES-D.

When multiple regression analyses were conducted, no dependent variable or combination of dependent variables emerged as a significant predictor of IL-6 concentrations at either baseline or 8weeks.

In fact, HardiAttitudes scores, rather than emerging as the strongest predictor of IL-6 levels at both baseline and 8-weeks, were the weakest predictors. This hypothesis was based on the concept of coping as discussed by Lazarus and Folkman (1984) and others, and the conceptual similarities between coping and hardiness. Lazarus and Folkman emphasized the value of problem-focused coping strategies versus emotionally-based coping. The problem-focused strategies are similar to those used in problem solving: initially defining the problem, generating alternatives, weighing the alternative cost and

benefits, choosing, and acting. The choice of the coping strategy is viewed as dependant on the nature of the stressor.

In contrast to the transactional model of coping and stress advanced by Lazarus and Folkman (1980) is hardiness, conceived of as a personality disposition. It was originally formulated as a set of attitudes motivating an individual to respond to stressful circumstances in an adaptive manner (Kobasa, 1979), as a buffer between stress and illness, and as an inherent tendency towards health in stressful environments. Hardiness enables one to tolerate the anxiety of uncertainty (Maddi, 2004), and provides the motivation to actively change disaster into opportunity (Kobasa, 1979; Maddi & Kobasa, 1982; Maddi, 2004). Through commitment, control, and challenge (the 3 C's), individuals look to involvement with others to find experience and meaning, avoid alienation and isolation, and have the desire and willingness to struggle to influence the outcomes concerning them. Finally, they view struggle to learn and grow from any experience “developmentally fulfilling”(Maddi, 2004). Yet, in this study, HardiAttitudes had the least strength as a predictor variable in the multiple regression model, ranking last behind POMS TMD and CES-D scores.

Intent-to-treat analysis

The intent-to-treat format is typically employed in randomized medical clinical trials and is designed to address the issue that any difference between groups that arises after randomization could be due to the consequences of the randomized treatment assignment. That is, if noncompliance (i.e., withdrawal) with treatment occurs after randomization, it may be due to the treatment itself. Exclusion of noncompliant participants from the

analysis can bias the treatment evaluation. Therefore, intent-to-treat analysis includes all randomized participants in the groups to which they were originally randomly assigned, regardless of whether treatment was actually received or the participant withdrew from the study (LaValley, 2003).

In the case of ADRD patients and their caregivers, the burden of the time required to receive treatment may be sufficiently onerous to the already overburdened caregivers that they simply drop out. In fact, this phenomenon has been discussed in the caregiving literature. Researchers have noted that some caregivers, even while acknowledging their need for treatment and the likely effectiveness of that treatment, state that they simply “don’t have the time for this”. This statement is not uncommon even when respite services are offered to enable the caregiver to participate in treatment (Brodaty, Thomson, Thompson, & Fine, 2005). However, it was because of the extension of intent-to-treat principles to this study that it was decided to take a conservative approach and conduct initial analyses on multiple participant groups. The results of those analyses showed that there were no significant differences among groups, and therefore, the remainder of the study analyses were conducted on the group ($N = 18$) that had all of their psychosocial and biomarker data intact.

Limitations of this study

The limitations impacting this study were several. As already emphasized, recruitment and assay difficulties yielded a small sample size and lack of statistical power. The fact that the group leaders were not blind to the study hypotheses was a serious concern, particularly inasmuch as the study author was one of the group leaders.

Furthermore, it is possible that differing levels of skill and experience among the group leaders influenced the obtained data, even though analysis indicated there were no significant differences between groups by location on their dependent variables.

Two demographic limiters of note were gender and race. All participants in the study were female, and only one out of twenty-four was not Caucasian. The homogeneity of the participants obviously limits the generalizability of this study.

Conclusions

No published studies have used Interleukin-6 as a dependent variable in a controlled trial of a cognitive behavioral intervention with familial caregivers. This study found no significant change in IL-6 levels that could be attributed to the intervention, and no significant correlation between IL-6 concentrations and any of the other dependent variables at either baseline or 8-weeks. However, significant change did occur on several psychosocial measures, most notably and consistently on measures of depression, but also on a more global measure of caregiver distress, the TMD of the POMS. As previously noted, that places this study in the minority of caregiver studies conducting controlled clinical intervention trials.

Taking into account the methodological and statistical limitations of this study, only qualified conclusions can be drawn. It is interesting to note, however, that both group leaders subjectively reported that the participants in the CBSM group became very close to one another over the 8-week time span of the treatment intervention. Uchino et al. (1996) note that one of the most robust findings in the psychoneuroimmunological literature (PNI) is the link between personal relationships and immune function. That link

was not objectively established in this study. However, the stress-moderating effects of social support have been noted by a number of researchers (Koenig, et al., 1997; Fawzy, et al., 1993; Spiegel, 1989) and may have had an impact in this study as evidenced by the significant change in depression measure scores obtained.

Recommendations

It would be useful for further work to be done that explores the efficacy of psychosocial interventions with familial ADRD caregivers. Studies that are well controlled, with longitudinal designs that employ manual specified interventions with standardized intervention delivery protocols would be most appropriate. They should include sample sizes sufficient to generate power at the recommended .8 level, with gender and ethnic diversity among participants. Ideally, participants would include caregivers matched with noncaregivers. Dependent measures might include IL-6, as its significance is well established, but additional biomarkers known to be more rapid responders to change, such as cortisol levels, or vaccination response rates, would also be desirable. As an example, the previously cited Japanese caregiver study (Hosaka & Sugiyama, 2003) that employed both the POMS and a biomarker as a dependent variable, found a significant difference in their biomarker (augmentation of NK cell activity) at the end of their 5th session, approximately 5 weeks post-baseline.

REFERENCES

- Abel, E. K. (1987). *Love is not enough: Family care of the frail elderly*. Washington, D.C.: American Public Health Association.
- Ackerman, K. D., Bellinger, D. L., Felten, S. Y., & Felton, D. L. (1991). Ontogeny and senescence of nonadrenergic innervation of the rodent thymus and spleen. In R. Ader, D. L. Felton, & N. Cohen (Eds.) *Psychoneuroimmunology* (2nd ed., pp 72-114) San Diego, CA: Academic Press.
- Ackerman, K. D., Martino, M., Heyman, R., Moyna, N. M., & Rabin, B. S. (1998). Stressor- induced alteration of cytokine production in multiple sclerosis patients and controls. *Psychosomatic Medicine*, 60, 484-491.
- Ader, R. (1983). Developmental Psychoneuroimmunology. *Developmental Psychobiology*, 16(4), 251-267.
- Advisory Panel on Alzheimer's Disease (1993). *Fourth report of the advisory panel on Alzheimer's Disease*. NIH Pub. No. 93-3520. Washington, DC:Supt. Of Docs. U.S. Government Printing Office.
- Aldwin, C., Folkman, S., Shaefer, C., Coyne, J., & Lazarus, R. (1980). *Ways of Coping Checklist: A process measure*. Paper presented at the annual American Psychological Association Meetings, Montreal, Canada.

- Almberg, B., Grafstrom, M., & Winblad, B. (1997). Major strain and coping strategies as reported by family members who care for aged demented relatives. *Journal of Advanced Nursing*, 26, 683-691.
- Altman, F. (1997). Where is the "Neuro" in Psychoneuroimmunology? A Commentary on Increasing research on the "Neuro" Component of Psychoneuroimmunology. *Brain, Behavior, and Immunity*, 11, 1-8.
- American Psychological Association (2000) *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*. (4th Ed., Text Revision). Washington, DC: American Psychiatric Association.
- Anderson, B. L., Farrar, W. B., Golden-Kreutz, D. M., Glaser, R., Emery, C. F., Crespin, T. R., Shapiro, C. L., & Carson, W. E. III. (2004). Psychological, behavioral, and immune changes after a psychological intervention. *Journal of Clinical Oncology*, 22 (17), 3570-3580.
- Anderson, B. L., Kiecolt-Glaser, J. K., & Glaser, R. (1994). A biobehavioral model of cancer stress and disease course. *American Psychologist*, 49, 389-404.
- Antoni, M. H. (1997). Cognitive-behavioral intervention for persons with HIV. In J. L. Spira (Ed.) *Group therapy for medically ill patients* (pp. 55-91). New York: Guilford Press.
- Antoni, M. H., Cruess, D. G., Cruess, S., Lutgendorf, S. K., Kumar, M., & Ironson, G., et al. (2000). Cognitive-behavioral stress management intervention effects on anxiety, 24-hr urinary norepinephrine output, and T-cytotoxic/suppressor cells over time among symptomatic HIV-infected gay men. *Journal of Consulting and Clinical Psychology*, 68, 31-45.

- Arnetz, B. B., Brenner, S. O., Levi, L., Hjelm, R., Petterson, I. L., Wasserman, J., et al., (1991). Neuroendocrine and immunologic effects of unemployment and job insecurity. *Psychotherapy and Psychosomatics*, 55, 76-80.
- Atienza, A.A., Henderson, B.A., Wilcox, S., & King, A.C. (2001). Gender Differences in Cardiovascular Response to Dementia Caregiving. *The Gerontologist*, 41(4), 490-498.
- Aubert, A., Vega, C., Dantzer, R., & Goodall, G. (1995). Pyrogens specifically disrupt the acquisition of a task involving cognitive processing in the rat. *Brain, Behavior, and Immunity*, 9, 129-148.
- Banks, W. A. (2001). Cytokine's CV's and the blood brain barrier. In R. Ader, D. L. Fenton, & N. When (Eds.), *Psychoneuroimmunology* (3rd ed., pp. 483-499). San Diego: Academic Press.
- Baron, R. S., Cutrona, C. E., Hicklen, D., Russell, D. W., & Lubaroff, D.M. (1990). Social support and immune function among spouses of cancer patients. *Journal of Personality and Social Psychology*, 59, 344-352.
- Bartone, P. T., Ursano, R. J., Wright, K. M., & Ingraham, L. H. (1989). The impact of a military air disaster on the health of assistance workers: A prospective study. *Journal of Nervous and Mental Disease*, 177, 317-328.
- Bauer, M. E., Vedhara, K., Perks, P., Wilcock, G. K., Lightman, S. L., & Shanks, N. (2000). Chronic stress in caregivers of dementia patients is associated with reduced lymphocyte sensitivity to glucocorticoids. *Journal of Neuroimmunology*, 103, 84-92.

- Baum, A., Cohen, L., & Hall, M. (1993). Control and intrusive memories as possible determinants of chronic stress. *Psychosomatic Medicine*, 55, 274-286.
- Baumann, H., & Gauldie, J. (1994). The acute phase response. *Immunology Today*, 15, 74-81.
- Beatty, J. (2001). *The Human Brain: Essentials of Behavioral Neuroscience*. Sage Publications: Thousand Oaks, CA.
- Belle, S.H., Czaja, S.J., Schulz, R., Zhang, S., Burgio, L.D., Gitlin, L.N., Jones, R., Mendelsohn, A.B., & Ory, M.G. (2003). Using a new Taxonomy to combine the uncombinable: Integrating results across Diverse Interventions. *Psychology and Aging*, 18(3), 396-405.
- Blalock, J.E., Smith, E. M., & Meyer, W. J. (1985). The pituitary-adrenocortical axis and the immune system. *Clinics in Endocrinology and Metabolism*, 14, 1021-1038.
- Blatteis, C. M. (1992). Role of the OVLT in the febrile response to circulating pyrogens. *Progress in Brain Research*, 91, 409-412.
- Blazer, D. G. (1994). Geriatric Psychiatry. In R. E. Hales, S. C. Yudofsky, & J. A. Talbott (Eds.). *The American psychiatric Press Textbook of Psychiatry* (2nd ed., pp. 1405-1421. Washington, DC: American Psychiatric Press.
- Bodnar, J., & Kiecolt-Glaser, J. K. (1994). Caregiver depression after bereavement: Chronic stress isn't over when it's over. *Psychology and Aging*, 9, 372-380.
- Boesen, E. H., Ross, L., Frederiksen, K., Thomsen, B. L., Dahistrom, K., Schmidt, G. et al. (2005). Psychoeducational intervention for patients with cutaneous malignant melanoma: A replication study. *Journal of Clinical Oncology*, 23 (6), 1270-1277.

- Bovbjerg, D. H., Redd, W. H., Maier, L. A., Holland, J. C., Lesko, L. M., Niedzwiecki, D., et al. (1990). Anticipatory immune suppression and nausea in women receiving cyclic chemotherapy for ovarian cancer. *Journal of Consulting and Clinical Psychology*, 58, 153-157.
- Brodaty, H., Green, A., & Koschera, A. (2003) Meta-Analysis of Psychosocial Interventions for Caregivers of People with Dementia. *Journal of the American Geriatrics Society*, 51(5), 657-664.
- Brodaty, H., Gresham, M., & Luscombe, G. (1997). The Prince Henry Hospital dementia caregivers' training programme. *International Journal of Geriatric Psychiatry. Special Issue: Geriatric Psychiatry in Australia*, 12(2), 183-192 .
- Brodaty, H., Thomson, C., Thompson, C., & Fine, M. (2005). Why caregivers of people with dementia and memory loss don't use services. *International Journal of Geriatric Psychiatry*, 20, 537-546.
- Brodaty, H., Roberts, K., & Peters, K. (1994). Quasi-Experimental evaluation of an educational model for dementia caregivers. *International Journal of Geriatric Psychiatry*, 9, 195-204.
- Brookmeyer, R., & Gray, S. (2000). Methods for projecting the incidence and prevalence of chronic diseases in ageing populations: application to Alzheimer's disease. *Stat Med*, 19, 1481-93.
- Buckwalter, K. C., Gerdner, L., Kohout, F., Hall, G. R., Kelly, A., Richards, B., & Sime, M. (1999). A nursing intervention to decrease depression in family caregivers of persons with dementia. *Archives of Psychiatric Nursing*, 13(2), 80-88.

- Burgio, L., Corcoran, M., Lichstein, K.L., Nichols, L., Czaja, S., Gallagher-Thompson, D., Bourgeois, M., Stevens, A., Ory, M., & Schulz, R. (2001). Judging Outcomes in Psychosocial Interventions for Dementia Caregivers: The Problem of Treatment Implementation. *The Gerontologist*, 41(4), 481-489.
- Burleson, M. H., Poehlmann, K. M., Hawkley, L. C., Ernst, J. M., Berntson, G. G., Malarkey, W. B., Kiecolt-Glaser, J. K., Glaser, R., & Cacioppo, J. T. (2003). Neuroendocrine and cardiovascular reactivity to stress in mid-aged and older women: Long-term temporal consistency of individual differences. *Psychophysiology*, 40, 358-369.
- Burleson, M. H., Poehlmann, K. M., Hawkley, L. C., Ernst, J. M., Berntson, G.G., Malarkey, W. B., Kiecolt-Glaser, J. K., Glaser, R., & Cacioppo, J. T. (2002). Stress-related immune changes in mid-aged and older women: One-year consistency of individual differences. *Health Psychology*, 21, 321-331.
- Burns, E. A., & Goodwin, J.S. (1990). *Immunology and Infectious Disease*. In C. K. Cassel, D. E. Risenberg, L. B. Sorensen & J. R. Walsh (Eds.). *Geriatric Medicine* (pp. 312-329). New York: Springer-Verlag.
- Butcher, H.K., Holkup, P.A., Coen-Buckwalter, K. (2001). The Experience of Caring for a Family Member with Alzheimer's Disease. *Western Journal of Nursing Research*, 23(1), 33-55.
- Cacioppo, J. T., Kiecolt-Glaser, J. K., Malarkey, W. B., Kutz, L. A., Poehlmann, K. M., Burleson, M. H., & Glaser, R. (2002). Autonomic and glucocorticoid associations with the steady state expression of latent Epstein-Barr virus. *Hormones and Behavior*, 42, 32-41.

- Cacioppo, J. T., Malarkey, W. B., Kiecolt-Glaser, J. K., Uchino, B. N., Sgoutas-Emch, S. A., Sheridan, J. F., Berntson, G. G., & Glaser, R. (1995). Heterogeneity in Neuroendocrine and Immune Responses to Brief Psychological Stressors as a Function of Autonomic Cardiac Activation. *Psychosomatic Medicine*, 57(2), 154-164.
- Cacioppo, J. T., Poehlmann, K. M., Kiecolt-Glaser, J. K., Malarkey, W. B., Burleson, M., Berntson, G.G. & Glaser, R. (1998). Cellular immune responses to acute stress in female caregivers of dementia patients and matched controls. *Health Psychology*, 17, 182-189.
- Cacioppo, R., Berntson, G. G., Malarkey, W. B., Kiecolt-Glaser, J. K., Sheridan, J. F., Poehlmann, K. M., Burleson, M. H., Ernst, J. M., Hawkley, L. C., & Glaser, R. (1998). Autonomic, neuroendocrine, and immune responses to psychological stress: The reactivity hypothesis. *Annals of the New York Academy of Sciences* 840, 664-673.
- Calero, M.D., Arnedo, M.L., Navarro, E., Ruiz-Pedrosa, M., & Canero, C. (2002). Usefulness of a 15 Item Version of the Boston Naming Test in Neuropsychological Assessment of Low-Educational Elders with Dementia. *Journal of Gerontology*, 57B (2), 187-191.
- Castle, S., Wilkens, S., Heck, E., Tanzy, K., & Fahey, J. (1995). Depression in caregivers of demented patients is associated with altered immunity: Impaired proliferative capacity, increased CD8+, and a decline in lymphocytes with surface signal transduction molecules (CD38) and a cytotoxicity marker (CD56+CD8+). *Clinical and Experimental Immunology*, 101, 487-493.

- Catania, A., Airaghi, L., Motta, P., Manfredi, M. G., Annoni, K., Pettenati, C., et al., (1997). Cytokine antagonists in aged subjects and their relation with cellular immunity. *Journals of Gerontology: Biological Sciences and Medical Sciences*, 52A, B93-97.
- Chang, B. L. (1999). Cognitive-Behavioral Intervention for Homebound Caregivers of Persons with Dementia. *Nursing Research*, 48(3), 173-182.
- Charlesworth, G. M. (2001). Reviewing psychosocial interventions for family cares of people with dementia, *Aging and Mental Health*, 5(2), 104-106.
- Christensen, A. J., Edwards, D. L., Wiebe, J. S., Benotsch, E. G., McKelvey, L., Andrews, M., & Lubaroff, D. M. (1996). Effect of verbal self-disclosure on natural killer cell activity: Moderating influence of cynical hostility. *Psychosomatic Medicine*, 58, 150-155.
- Clarke, P. C. Effects of Individual and Family Hardiness on Caregiver depression and fatigue. *Research in Nursing & Health*, 25(3), 37-48.
- Clyburn, L. D., Stones, M. J., Hadjistavropoullus, T., Tuokko, H. (2000). Predicting caregiver burden and depression in Alzheimer's Disease. *Journal of Gerontology*, 55B (1), S2-S13.
- Cobb, S. (1976). Social support as a moderator of life stress. *Psychosomatic Medicine*, 38(5), 300-314.
- Coe, C. L. (1993). Psychosocial factors and immunity in nonhuman primates: A review. *Psychosomatic Medicine*, 55, 298-308.
- Cohen, H. J. (2000). Editorial: In search of the underlying mechanism of frailty. *Journals of Gerontology: Biological Sciences and Medical Sciences*, 55A, M706-M708.

- Cohen, H. J., Pieper, C. F., Harris, T., Rao, K. M. K., & Currie, M. S. (1997). The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *Journals of Gerontology: Biological Sciences and Medical Sciences*, 55A, M706-M708.
- Cohen, N. (2006). The uses and abuses of Psychoneuroimmunology: A global overview. *Brain, Behavior, and Immunity*, 20, 99-112.
- Cohen, S., Doyle, W.J., & Skoner, D.P. (1999). Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosomatic Medicine*, 61, 175-180.
- Cohen, S., Doyle, W.J., Skoner, D.P., Rabin, B.S., & Gwaltney, J.M. (1997). Social ties and susceptibility to the common cold. *JAMA*, 277, 1940-1944.
- Cohen, S., Frank, E., Doyle, W.J., Skoner, D.P., Rabin, B.S., & Gwaltney, J.M. (1998). Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychology*, 17, 214-223.
- Cohen, S., Hamrick, N. (2003). Stable individual differences in physiological response to stressors: implications for stress-elicited changes in immune related health. *Brain, Behavior, and Immunity*, 17, 407-414.
- Cole, S. W., Kemeny, M., Taylor, S. E., Visscher, B., & Fahey, J. (1996). Accelerated course of human immunodeficiency virus infection in gay men who conceal their homosexual identity. *Psychosomatic Medicine*, 58, 219-231.
- Cook, J. M., Pearson, J. L., & Ahrens, A. H. (1997). General and specific events and depressive symptoms in Alzheimer's disease caregivers. *American Journal of Alzheimer's Disease*, 12, 32-34.

- Cooke, D. D., McNally, L., Mulligan, K. T., Harrison, M. J. G., & Newman, S. (2001). Psychosocial interventions for caregivers of people with dementia: a systematic review. *Aging and Mental Health*, 5(2), 120-135.
- Cunningham, A. J., Edmonds, C. B. I., Jenkins, G. P., Pollack, H., Lockwood, G. A., & Warr, D. (1998). A randomized controlled clinical trial of the effects of group psychological therapy on survival in women with metastatic breast cancer. *Psycho-Oncology*, 7, 508-517.
- Cunningham, E. T., de Souza, E. B. (1993). Interleukin-1 receptors in the brain and endocrine tissues. *Immunology Today*, 14, 171-176.
- Dantzer, R. (1994). Stress and Immunity: what have we learned from psychoneuroimmunology? *Neurobiologie Integrative Inserm U394*, Bordeaux, France.
- Davidson, R. J., Jackson, D. C., & Kalin, N.H. (2000). Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. *Psychological Bulletin*, 126, 890-909.
- Davidson, R. J., Coe, C. C., Dolski, I., & Donzella, B. (1999). Individual differences in prefrontal activation asymmetry predict natural killer cell activity at rest and in response to challenge. *Brain, Behavior, and Immunity*, 13, 93-108.
- Davidson, R. J., Kalin, N. H., Schumacher, J., Rosenkranz, M., Muller, D., Santorelli, S. F., Urbanowski, F., Harrington, A., Bonus, K., & Sheridan, J. F. (2003). Alterations in brain and immune function produced by mindfulness meditation. *Psychosomatic Medicine*, 65, 564-570.

- Day, A. T. (1985). Who cares? Demographic trends challenge family care for the elderly. *Population Trends and Public Policy*, 9, 1-17.
- Dean, A., Lin, N. (1977). The stress-buffering role of social support. *Journal of Nervous & Mental Disease*, 165(6), 403-417.
- Dekaris, D., Sabioncello, A., Mazuran, R., Rabatic, S., Svoboda-Beusan, L., Racunica, N.L., & Tomasic, J., (1993). Multiple changes of immunological parameters in prisoners of war. *JAMA*, 270, 595-599.
- Dentino, A. N., Pieper, C. F., Rao, K. M. K., Currie, M., S., Harris, T., Blazer, D. G., & Cohen, H. J. (1999). Association of interleukin-6 and other biologic variables with depression in older people living in the community. *Journal of the American Geriatrics Society*, 47, 6-11.
- Desbiens, N.A., Myeller-Rizner, N., Virnig, B., & Lynn, J. (2001). Stress in Caregivers of hospitalized Oldest-Old Patients. *Journal of Gerontology*, 56 A(4), 231-235.
- Dhabhar, F.S., & McEwen, B. S. (1997). Enhancing versus suppressive effects of stress hormones on skin immune function. *Proceedings of the National Academy of Science USA*, 96, 1059-1064.
- DiBartolo, M. C., Soeken, K. L. (2003). Appraisal, coping, hardiness, and self-perceived health in community-dwelling spouse caregivers of persons with dementia. *Research in Nursing & Health*, 26, 445-458.
- Dilworth-Anderson, P., Canty-Williams, I., & Gibson, B.E. (2002). Issues of Race, Ethnicity, and Culture in Caregiving Research: A 20-Year Review. *The Gerontologist*, 42(2), 237-272.

- Dolbier, C. L., Cocke, R. R., Leiferman, H. A., Steinhardt, M.A., Schapiro, S. J., Nehete, P. N., Perlman, J. E., & Sastry, J., (2001). Differences in functional immune responses of high vs. low hardy health individuals. *Journal of Behavioral Medicine*, 24 (3), 219-229.
- Dorland, W.A. (1985). *Dorland's Illustrated Medical Dictionary*, 26th edition. Philadelphia : W.B. Saunders Company.
- Doty, P. (1986). Family care of the elderly: The role of public policy. *Milbank Quarterly*, 64, 34-75.
- Dunkin, J. J., & Hanley, C. A. (1998). Dementia caregiver burden: A review of the literature and guidelines for assessment and intervention. *Neurology*, 51 (Suppl. 1), S53-S60.
- Dunn, A. J. (1995). Interactions between the nervous system and the immune system: Implications for psychopharmacology. In F. E. Bloom & D. J. Kupfer (Eds.). *Psychopharmacology: The fourth generation of progress* (pp. 719-733). New York: Raven Press.
- Dura, J. R., Stukenberg, K. W., & Kiecolt-Glaser, J. K. (1991). Anxiety and depressive disorders in adult children caring for demented parents. *Psychology and Aging*, 6, 467-473.
- Dura, J., Stukenberg, K., & Kiecolt-Glaser, J. K. (1990). Chronic stress and depressive disorders in older adults. *Journal of Abnormal Psychology*, 99, 284-290.
- Epel, E. S., McEwen, B. S., Ickovics, J. R. (1998). Embodying Physiological Thriving: Physical thriving in response to stress. *Journal of Social Issues*, 54(2), 301-322.

- Ershler, W., & Keller, E. (2000). Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annual Review of Medicine*, 51, 245-270.
- Espel, E. S., Blackburn, E. H., Jue Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D. & Cawthon, R.M. (2004). Accelerated telomere shortening in response to life stress, *Proceedings of the National Academy of Science*, 101, 17312–17315.
- Esterling, B. A., Antoni, M. H., Fletcher, M. A., Margulies, S., & Schneiderman, N. (1994). Emotional disclosure through writing or speaking modulates latent Epstein-Barr virus antibody titers. *Journal of Consulting and Clinical Psychology*, 62, 130-140.
- Esterling, B. A., Kiecolt-Glaser, J. K., Bodnar, J., & Glaser, R. (1994). Chronic Stress, Social Support, and Persistent Alterations in the Natural Killer Cell Response to Cytokines in Older Adults. *Health Psychology*, 13, 291-299.
- Fahdi, I. E., Gaddam, V., Garza, L., Romeo, F. & Mehta, J. L. (2003). Inflammation, infection, and atherosclerosis. *Brain, Behavior, and Immunity*, 17, 238-244.
- Fawzy, F. I., Canada, A. L., Fawzy, N. W., (2003). Malignant Melanoma: Effects of a brief, structured psychiatric intervention on survival and recurrence at 10-year follow-up. *Archives of General Psychiatry*, 60, 100-103.
- Fawzy, F. I., Fawzy, N. W., Hyun, C. S., Elashoff, R., Guthrie, D., Fahey, J. L., & Morton, D. L. (1993). Malignant melanoma: Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. *Archives of General Psychiatry*, 50, 681-689.

- Ferrucci, L., Harris, T., Guralnik, J., Traci, R., Corti, M., Cohen, H., et al., (1999). Serum IL-6 level and the development of disability in older persons. *Journal of the American Geriatrics Society*, 47, 639-646.
- Finch, J. F., Okun, M. A., Barrera, Ma., Zautra, A. J., et al. (1989). Positive and negative social ties among older adults: Measurement models and the prediction of psychological distress and well-being. *American Journal of Community Psychology*, 17(5), 585-605.
- Fisher, L. D., Dixon, D. O., Herson, J., Frankowski, R. F., Hearn, M. S., Peace, K. E. (1990). *Intention to treat in clinical trials*. In: K. E. Peace (Ed), Statistical Issues in Drug Research and Development (pp 331-350). New York: Marcel Dekker, Inc.
- Fleshner, M., Goehler, L. E., Hermann, J., Relton, J. K., Watkins, L. R., & Maier, S. F. (1995). Interleukin-1b induced corticosterone elevation and hypothalamic NE depletion is vagally mediated. *Brain Research Bulletin*, 37, 605-610.
- Folkman, S., Schaeffer, C., & Lazarus, R. (1979). *Cognitive processes as mediators of stress and coping*. In V. Hamilton & D. Warburton (Eds.), Human stress and cognition (pp. 265-298). Chichester, England: Wiley.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189-198.
- Frankenhauser, M. (1986). A psychobiological framework for research on human stress and coping. In M.H. Appley & R. Trumbull (Eds.), *Dynamics of Stress*:

Physiological, psychological, and social perspectives (pp. 101-116). New York: Plenum.

Gallagher, T. J., Wagenfield, M. O., Baro, F., & Haepers, K. (1994). Sense of coherence, coping and caregiver role overload. *Social Science and Medicine*, 39, 1615-1622.

Gallagher-Thompson, D., Robinson Shurgot, G., Rider, K., Gray, H. L., McKibben, C. L., Kraemer, H. C., Sephton, S. S. & Thompson, L. W. (2006). Ethnicity, stress, and cortisol function in Hispanic and Non-Hispanic white women: A preliminary study of family dementia caregivers and noncaregivers. *American Journal of Geriatric Psychiatry*, 14 (4), 334-342.

Garand, L. (2000). *Psychoimmunological outcomes of a dementia caregiver intervention: The progressively lowered stress threshold*. Unpublished doctoral dissertation. University of Iowa.

Garand, L., Buckwalter, K. C., Lubaroff, D., Tripp-Reimer, T., Frantz, R. A., & Ansley, T. N. (2002). A pilot study of immune and mood outcomes of a community based intervention for dementia caregivers: The PLST intervention. *Archives of Psychiatric Nursing*, 16 (4), 156-167.

Geis, A., Rohleder, N., & Anton, F. (2006). Does a disturbed HPA axis function require enhanced IL-6 levels? Evidence from a psychoneuroimmunological study in fibromyalgia patients. *Brain, Behavior, and Immunity*, 20, 23-24.

Gitlin, L. N., Belle, S. H., Burgio, L. D., Czaja, S. J., Mahoney, D., Gallagher-Thompson, D., Burns, R., Hauck, W. W., Zhang, S., Schulz, R., & Ory, M. (2003) Effect of Multicomponent Interventions on Caregiver Burden and Depression: The REACH multisite initiative at 6-month follow-up. *Psychology and Aging*, 18 (3), 361-374.

- Gitlin, L. N., Winter, L., Dennis, M. P., Corcoran, M., Schinfeld, S., & Hauck, W. W. (2002). Strategies used by families to simplify tasks for individuals with Alzheimer's Disease and related disorders: Psychometric Analysis of the Task Management Strategy Index (TMSI). *The Gerontologist*, 42(1), 61-69.
- Glaser, R. & Kiecolt-Glaser, J. K. (1998). Stress-associated immune modulation: Relevance to viral infections and chronic fatigue syndrome. *American Journal of Medicine*, 105(3A), 35s-42s
- Glaser, R. & Kiecolt-Glaser, J. K. (Eds.). (1994). *Handbook of human stress and immunity*. San Diego, CA: Academic Press.
- Glaser, R., Kiecolt-Glaser, J. K., Malarkey, W. B., Kennedy, S., & Hughes, J. (1992). Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. *Psychosomatic Medicine*, 54, 22-29.
- Glaser, R., Kiecolt-Glaser, J. K., Marucha, P. T., MacCallum, R. C., Laskowski, B. F., & Malarkey, W. B. (1999). Stress-related changes in proinflammatory cytokine production in wounds. *Archives of General Psychiatry*, 56, 450-456.
- Glaser, R., Kiecolt-Glaser, J.K., Malarkey, W. B., & Sheridan, J.F. (1998). The influence of psychological stress on the immune response to vaccines. *Annals of the New York Academy of Sciences* 840, 665-663.
- Glaser, R., MacCallum, R.C., Laskowski, B.S., Malarkey, W.B., Sheridan, J.F., & Kiecolt-Glaser, J.K. (2001). Evidence for a shift in the Th-1 to Th-2 cytokine response associated with chronic stress and aging. *Journal of Gerontology: Medical Sciences*, 56, M477-M482.

- Glaser, R., Robles, T. F., Sheridan, J. F., Malarkey, W. B., & Kiecolt-Glaser, J. K. (2003). Mild depressive symptoms are associated with amplified and prolonged inflammatory responses following influenza vaccination in older adults. *Archives of General Psychiatry*, 60, 1009-1014.
- Glaser, R., Sheridan, J. F., Malarkey, W. B., MacCallum, R. C., & Kiecolt-Glaser, J. K. (2000). Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosomatic Medicine*, 62, 804-807.
- Goode, K. T., Hlaey, W. E., Roth, D. L., & Ford, G. R. (1998). Predicting longitudinal changes in caregiver physical and mental health: A stress process model. *Health Psychology*, 17, 190-198.
- Gottlieb, B. H., & Cignac, M. A. M. (1996). Content and domain specificity of coping among family caregivers of persons with dementia. *Journal of Aging Studies*, 10, 137-155.
- Grant, I., Adler, K. A., Patterson, T. L., Dimsdale, J. E., Ziegler, M. G., & Irwin, M. R. (2002). Health Consequences of Alzheimer's Caregiving Transitions: Effects of Placement and Bereavement. *Psychosomatic Medicine*, 64(3), 477-486.
- Grant, I., McKibbin, C. L., Taylor, M. J., Mills, P., Dimsdale, J., Ziegler, M., & Patterson, T. L. (2003). In home respite intervention reduces plasma epinephrine in stressed Alzheimer caregivers. *American Journal of Geriatric Psychiatry*, 11(1), 62-72.
- Grant, R.W. (2001). Stress Inventories used in Clinical and Non-Clinical Settings. In *Eating Disorders in Women and Children: Prevention, Stress Management, and*

- Treatment* (pp. 147-161). Robert-McComb, J. J. (Ed.). Boca Raton, FL, US: CRC Press.
- Guidi, L., Tricerri, A., Frasca, D., Vangeli, M., Errani, A.R., & Bartolini, C. (1998). Psychoneuroimmunology and Aging. *Gerontology*, 44, 247-261.
- Hadjiconstantinou, M., McGuire, L., Duchemin, A., Laskowski, B., Kiecolt-Glaser, J. K., & Glaser, R. (2001). Changes in plasma nerve growth factor levels in older adults associated with chronic stress. *Journal of Neuroimmunology*, 116, 102-106.
- Haley, W. E., Roth D. L., Coleton, M. I., Ford, G. R., West, G. A., Collins, R. P., & Isobe, T. L. (1996). Appraisal, coping, and social support as mediators of well being in black and white family caregivers of patients with Alzheimer's disease. *Journal of Consulting and Clinical Psychology*, 64, 121-129.
- Hammerman, D. (1999). Toward an understanding of frailty. *Annals of internal medicine*, 130(June 1), 945-950.
- Harris, T., Ferrucci, L., Tracy, R., Corti, M., Wacholder, S., Ettinger, W. J., et al., (1999). Association of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *American Journal of Medicine*, 106, 506-512.
- Hart, B. L. (1988). Biological basis of the behavior of sick animals. *Neuroscience and Biobehavioral Reviews*, 12, 123-137.
- Hawkey, L. C., Cacioppo, J. T. (2004). Stress and the aging immune system. *Brain, Behavior, and Immunity*, 18, 114-119.
- Hebert, R., Leclerc, G., Bravo, G., Girouard, D., & Lefrancois, R. (1994). *Archives of Gerontology and Geriatrics*, 18, 1-14.

- Heffner, K. L., Loving, T. J., Robles, T. F., & Kiecolt-Glaser, J. K. (2003). Examining psychosocial factors related to cancer incidence and progression: In search of the silver lining. *Brain, Behavior, and Immunity*, 17 (Supplement 1), 109-111.
- Hepburn, K. W., Tornatore, J., Center, B., & Ostwald, S. W. (2001). Dementia Family Caregiver Training: Affecting Beliefs About Caregiving and Caregiver Outcomes. *Journal of the American Geriatrics Society*, 49, 450-457.
- Herberman, R. B. (2001). Immunotherapy. In R. E. Lenhard Jr., R. T. Osteen, & T. Gansler (Eds.) *Clinical Oncology* (pp.215-223). Atlanta, GA: American Cancer Society.
- Herbert, T. B., & Cohen, S. (1993a). Stress and immunity in humans: A meta-analytic review. *Psychosomatic Medicine*, 55, 364-379.
- Herbert, T. B., & Cohen, S. (1993b). Depression and immunity: A meta-analytic review. *Psychological Bulletin*, 113 (3), 472-486.
- Hinchliffe, A. C., Hyman, I. L., Blizard, B., & Livingston, G. (1995). Behavioural complications of dementia-can they be treated? *International Journal of Geriatric Psychiatry*, 10, 839-847.
- Hinrichsen, G. H., & Niederehe, G. (1994). Dementia management strategies and adjustment of family members of older patients. *The Gerontologist*, 34, 95-102.
- Hong, S. (2000). Exercise and Psychoneuroimmunology. *International Journal of Sport Psychology*, 31, 204-227.
- Hooker, K., Monahan, D. J., Bowman, S. R., Frazier, L. D., Shifren, K. (1998). Personality counts for a lot: Predictors of mental and physical health of spouse caregivers in two disease Groups. *Journal of Gerontology*, 53B (2), P73-85.

- Hosaka, T. & Sugiyama, Y (2003). Structured intervention in family caregivers of the demented elderly and changes in their immune function. *Psychiatric and Clinical Neurosciences*, 57 (2), 147-151.
- House, J.S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science*, 241, 540-545.
- House, J.S., Umberson, D., & Landis, K. R., (1988). Structures and Processes of social support. *Annual Review of Sociology*, 14, 293-318.
- Ironson, G., Wynings, C., Schneiderman, N, Baum, A., Rodriguez, M., Greenwood, D., et al., (1997). Posttraumatic stress symptoms, intrusive thoughts, loss and immune function after Hurricane Andrew. *Psychosomatic Medicine*, 59, 128-141.
- Irwin, M., Brown, M., Patterson, T., Hauger, R., Mascovich, A., & Grant, I. (1991). Neuropeptide Y and natural killer cell activity: Findings in depression and Alzheimer caregiver stress. *FASEB Journal*, 5, 3100-3107.
- Irwin, M., Rinetti, G., Redwine, L., Motivala, S., Dang, J. & Ehlers, C. (2004). Nocturnal proinflammatory cytokine-associated sleep disturbances in abstinent African American alcoholics. *Brain, Behavior, and Immunity*, 18, 349-360.
- Irwin, M. R., Pike, J. L., Cole, J. C. & Oxman, M. D. (2003). Effects of a behavioral intervention, Tai Chi Chuan, on varicella-zoster virus-specific immunity and health functioning in older adults, *Psychosomatic Medicine*, 65, 824-830.
- Jabaaij, P. M., Grosheide, P. M., Heijtkink, R. A., Duivenvoorden, H. J., Ballieyx, R. E., & Vingerhoets, A. J. J. M. (1993). Influence of perceived psychological stress and distress on antibody response to low dose rDNA hepatitis B vaccine, *Journal of Psychosomatic Research*, 37, 361-369.

- Jaloweic, A., Murphy, S., & Powers, M. (1984). Psychometric assessment of the Jaloweic Coping Scale. *Nursing Research*, 33, 157-161.
- Janevic, M.R., Connell, C.M. (2001). Racial, Ethnic, and Cultural Differences in the Dementia Caregiving Experience: Recent Findings. *The Gerontologist*, 41(3), 334-347.
- Jarrott, S.E., Zarit, S.H., Parris-Stephens, M.A., Townsend, A.L., Greene, R. (2000). Effects of Adult Day Service Programs on Time Usage by Employed and Non-Employed Caregivers. *The Journal of Applied Gerontology*, 19(4), 371-388.
- Jeong, I. (2004). *Effect of progressive muscle relaxation using biofeedback on perceived stress, stress response, immune response, and climacteric symptoms of middle aged women*. Department of Nursing, College of Medicine, Pusan National University.
- Kahan, J., Kemp, B., Staples, F. R. Brummel-Smith, K (1985). Decreasing the burden in families caring for a relative with a dementing illness: A controlled study. *Journal of the American Geriatrics Society*, 33(10), 664-670.:
- Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of illness in the aged, The Index of Activities of Daily Living: A standardized Measure of biological and psychosocial function. *Journal of the American Medical Association*, 185, 914-919.
- Kawakami, N., Tanigawa, T., Araki, S., Nakata, A., Sakurai, S., Yokoyama, K., & Morita, Y. (1997). Effects of job strain on helper-inducer (CD4+CD29) and suppressor-inducer (CD4+CD45RA) T cells in Japanese blue-collar workers. *Psychotherapy and Psychosomatics*, 66, 192-198.

- Kaye, J. M., Lawton, M. P., Gitlin, L. N., Kleban, M. H., Windson, L. A., & Kaye, D. (1988). Older people's performance on the Profile of Mood States (POMS). *Clinical Gerontologist*, 7, 35-36.
- Kaye, J., Morton, J., Maupin, D. (2000). Stress, Depression, and Psychoneuroimmunology. *Journal of Neuroscience Nursing*, 32(2), 93-100.
- Kazdin, A. E. (1998). *Research Design in Clinical Psychology*. Allyn and Bacon: Boston.
- Kelly, K. (2004). From hormones to immunity: the physiology of immunity. *Brain, Behavior, and Immunity*, 18, 95-113.
- Kemeny, M. E. (1994). Stressful events, psychological responses, and pregression of HIV infection. In R. Glaser & J. K. Kiecolt-Glaser (Eds.) *Handbook of Human Stress and Immunity* (pp. 245-266). San Diego, CA: Academic Press.
- Kemeny, M. E. (2003) An interdisciplinary research model to investigate psychosocial cofactors in disease: Application to HIV-1 pathogenesis. *Brain, behavior, and Immunity*:17 (1), S62-S72.
- Kemeny, M. E., Weiner, H., Duran, R., Taylor, S. E., Visscher, B., & Fahey, J. L. (1995). Immune system changes after the death of a partner in HIV-positive gay men. *Psychosomatic Medicine*, 57, 547-554.
- Kent, S., Bluthe, R. M., Kelley, K. W., & Dantzer, R. (1992). Sickness behavior as a new target for drug development. *Trends in Pharmacological Sciences*, 13, 24-28.
- Kiecolt-Glaser, J. K. (1999). Norman Cousins Memorial Lecture 1998. Stress, personal relationships, and immune function: health implications. *Brain, Behavior, and Immunity*, 13, 61-72.

- Kiecolt-Glaser, J. K., & Glaser, R. (1999c) Psychoneuroimmunology and cancer: Fact or fiction? *European Journal of Cancer*, 11, 1603-1607.
- Kiecolt-Glaser, J. K., & Glaser, R. (1988). Methodological issues in behavioral immunology research with humans. *Brain, Behavior, and Immunity*, 2, 67-78.
- Kiecolt-Glaser, J. K., & Glaser, R. (1991). Stress and Immune Function in Humans. In R. Ader, D. Felton, & N. Cohen (Eds.), *Psychoneuroimmunology*, (pp. 849-867). San Diego: Academic Press.
- Kiecolt-Glaser, J. K., & Glaser, R. (1995a). Measurement of immune response. In S. Cohen, R. Kessler, & L. G. Gordon (Eds.), *Measuring stress*, 213-229.
- Kiecolt-Glaser, J. K., & Glaser, R. (1999a). Chronic stress and mortality among older adults. *JAMA*, 282, 2259-2260.
- Kiecolt-Glaser, J. K., & Glaser, R. (1999b). Psychoneuroimmunology and immunotoxicology: Implications for carcinogenesis. *Psychosomatic Medicine*, 61, 271-272.
- Kiecolt-Glaser, J. K., & Glaser, R. (2001). Stress and immunity: Age enhances the risks. *Current Directions in Psychological Science*, 10, 18-21.
- Kiecolt-Glaser, J. K., & Glaser, R. (2002). Depression and immune function: Central pathways to morbidity and mortality. *Journal of Psychosomatic Research*, 53, 873-876.
- Kiecolt-Glaser, J. K., Bane, C., Glaser, R., & Malarkey, W. B. (2003). Love, marriage, and divorce: Newlyweds' stress hormones foreshadow relationship changes. *Journal of Consulting and Clinical Psychology*. 71, 176-188.

- Kiecolt-Glaser, J. K., Dura, J.R., Speicher, C.E., Trask, O.J., & Glaser, R. (1991). Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. *Psychosomatic Medicine*, 53, 345-362.
- Kiecolt-Glaser, J. K., Garner, W., Speicher, C. E., Penn, G., Holliday, J., & Glaser, R. (1984). Psychosocial modifiers of immunocompetence in medical students. *Psychosomatic Medicine*, 46, 7-14.
- Kiecolt-Glaser, J. K., Glaser, R. (1992). Psychoneuroimmunology: Can psychological interventions modulate immunity? *Journal of Consulting & Clinical Psychology. Special Issue: Behavioral medicine: An update for the 1990s. Vol 60(4)*, 569-575.
- Kiecolt-Glaser, J. K., Glaser, R. (1995b). Psychoneuroimmunology and Health Consequences: Data and Shared Mechanisms. *Psychosomatic Medicine*, 57(3), 269-274.
- Kiecolt-Glaser, J. K., Glaser, R., Cacioppo, J. T. & Malarkey, W. B. (1998). Marital stress: Immunologic, neuroendocrine, and autonomic correlates. *Annals of the New York Academy of Sciences* 840, 649-665.
- Kiecolt-Glaser, J. K., Glaser, R., Cacioppo, J. T., MacCallum, R. C., Snydersmith, M., Kim, C., Malarkey, W. B. (1997). Marital conflict in older adults: Endocrinological and immunological correlates. *Psychosomatic Medicine*, 59, 339-349.
- Kiecolt-Glaser, J. K., Glaser, R., Dyer, C., Shuttleworth, E., Ogrocki, P., & Speicher, C. E. (1987). Chronic Stress and immunity in family caregivers of Alzheimer's victims. *Psychosomatic Medicine*, 49, 523-535.

- Kiecolt-Glaser, J. K., Glaser, R., Gravenstein, S., Malarkey, W.B., & Sheridan, J. (1996). Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proceedings of the National Academy of Sciences, USA*, 93, 3043-3047.
- Kiecolt-Glaser, J. K., Glaser, R., Willinger, D., Stout, J., Messick, G., Sheppard, S., Ricker, D., Romisher, S. C., Briner, W., Bonnell, G. & Donnerberg, R. (1985). Psychosocial enhancement of immunocompetence in a geriatric population. *Health Psychology*, 4(1), 25-41.
- Kiecolt-Glaser, J. K., Malarkey, W.B., Cacioppo, J.T., & Glaser, R. (1994). Stressful personal relationships: Endocrine and immune function. In R. Glaser & J. K. Glaser (Eds.) *Handbook of human stress and immunity* (pp. 321-339). San Diego, CA. : Academic Press.
- Kiecolt-Glaser, J. K., Malarkey, W.B., Chee, M., Newton, T., Cacioppo, L. T., Mao, H. Y., & Glaser, R. (1993). Negative behavior during marital conflict is associated with immunological down-regulation. *Psychosomatic Medicine*, 55, 395-409.
- Kiecolt-Glaser, J. K., Marucha, P. T., Atkinson, C., & Glaser, R. (2001). Hypnosis as a modulator of cellular immune dysregulation during acute stress. *Journal of Consulting and Clinical Psychology*, 69, 674-682.
- Kiecolt-Glaser, J. K., Marucha, P.T., Malarkey, W. B., Mercado, A. M., & Glaser, R. (1995). Slowing of wound healing by psychological stress. *Lancet*, 346, 1194-1196.
- Kiecolt-Glaser, J. K., McGuire, L., Robles, T., & Glaser, R. (2002). Psychoneuroimmunology: Psychological influences on immune function and health. *Journal of Consulting and Clinical Psychology*. 70, 537-547.

- Kiecolt-Glaser, J. K., McGuire, L., Robles, T., & Glaser, R. (2002).
Psychoneuroimmunology and psychosomatic medicine: Back to the future.
Psychosomatic Medicine, 64, 15-28.
- Kiecolt-Glaser, J. K., Newton, T., Cacioppo, J. T., MacCallum, R.C., Glaser, R., &
Malarkey, W. B. (1996). Marital conflict and endocrine function: Are men really
more physiologically affected than women. *Journal of Consulting and Clinical
Psychology*, 64, 324-332.
- Kiecolt-Glaser, J. K., Preacher, K. J., MacCallum, R. C., Atkinson, C., Malarkey, W. B.,
& Glaser, R. (2003). Chronic stress and age-related increases in the
proinflammatory cytokine interleukin-6. *Proceedings of the National Academy
of Sciences, USA*.
- Kiecolt-Glaser, J. K., Ricker, D., George, J., Messick, G., Speicher, C. E., Garner, W., &
Glaser, R. (1984). Urinary cortisol levels, cellular immunocompetency, and
loneliness in psychiatric inpatients. *Psychosomatic Medicine*, 46, 15-24.
- Kiecolt-Glaser, J. K., Robles, T.F., Heffner, K.L., Loving, T.J., & Glaser, R. (2003).
Psycho-oncology and cancer: Psychoneuroimmunology and cancer. *Annals of
Oncology* 13 (Supplement 4), 166-169.
- Kiecolt-Glaser, J. K., Cacioppo, J.T., Malarkey, W.B., & Glaser, R. (1992). Acute
Psychological stressors and short-term immune changes: What, Why, for whom,
and to what extent? *Psychosomatic Medicine*, 54, 680-685.
- Kiecolt-Glaser, J.K. & Newton, T.L. (2001). Marriage and Health: His and hers.
Psychological Bulletin, 127, 472-503.

- Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., & Glaser, R. (2002). Emotions, Morbidity and Mortality: New Perspectives from Psychoneuroimmunology. *Annual Review of Psychology*, 53, 83-107.
- Kiecolt-Glaser, J.K., Page, G.G., Marucha, P.T., MacMallum, R.C., & Glaser, R. (1998), Psychological Influences on Surgical Recovery: Perspectives from Psychoneuroimmunology. *American Psychologist*, 53 (11), 1209-1218.
- Kneebone, I. I., & Martin, P. R. (2003). Coping and Caregivers of people with dementia. *British Journal of Health Psychology*, 8, 1-17.
- Kobasa, S. C. (1979). Stressful life events, personality, and health: An inquiry into hardiness. *Journal of Personality and Social Psychology*, 37, 1-11.
- Kobasa, S. C., & Maddi, S. R., & Kahn, S. (1982). Hardiness and health: A prospective study. *Journal of Personality and Social Psychology*, 42, 884-890.
- Kobasa, S.C. (1985). Stressful Life Events, Personality, and Health: An Inquiry into Hardiness. In *Stress and Coping*, 2nd edition (pp.175-188). R. S. Lazarus & A. Monat (Eds.) New York: Columbia University Press.
- Koenig, H. G., Cohen, H. J., George, L. K., Hays, J. C., Larson, D. B., Blazer, D. G. (1997). *Journal of Immunology*, 12, 233-250.
- Koenig, H.:G., Cohen, H.J., George, L.K., Hays, J.C., Larson, D.B., & Blazer, D.G.(1997). Attendance at Religious Services, Interleukin-6, and other Biological Parameters of Immune Function in Older Adults. *Journal of Immunology*, 12, 233-250.

- Kop, W. J. (2003). The integration of cardiovascular behavioral medicine and psychoneuroimmunology: New developments based on converging research fields. *Brain, Behavior, and Immunity*, *17*, 233-237.
- Kunkel, S. R., & Applebaum, R. A. (1992). Estimating the prevalence of long-term disability for an aging society. *Journal of Gerontology: Social Sciences*, *47*, S253-S260.
- La Via, M. F., Munno, I., Lydiard, R. B., Workman, E. W., Hubbard, J. R., Michel, Y., & Pauling, E. (1996). The influence of stress intrusion on immunodepression in generalized anxiety disorder patients and controls. *Psychosomatic Medicine*, *58*, 138-142.
- Landis, C. A., Lentz, M.J., Tsuji, J., Buchwald, D. & Shaver, J. L. F. (2004). Pain, psychological variables, sleep quality, and natural killer cell activity in midlife women and without fibromyalgia. *Brain, Behavior, and Immunity*, *18*, 304-313.
- Langer, E.J., Rodin, J.(1976). The Effects of Choice and Enhanced Personal Responsibility for the Aged: A Field Experiment in an Institutional Setting. *Journal of Personality and Social Psychology*, *34* (2), 191-198.
- Lanquillon, S., Krieg, J. C., & Vedder, H. (2000). Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*, *22*, 370-379.
- Larazus, R. S., & Folkman, S. (1984). *Stress, appraisal and coping*. New York: Springer.
- Lawton, M.P., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist*, *9*, 179-186.

- Lazarus, R., & Launier, R. (1978). Stress-related transactions between persons and environment, In L. Pervin & M. Lewis (Eds.), *Perspectives in international psychology* (pp. 287-325). New York: Plenum Press.
- Lee, K. W. J., Hill, J. S., Walley, K. R. & Frohlich, J. J. (2006). Relative risk factors of multiple plasma biomarkers as risk factors for coronary artery disease and death in an angiography cohort. *Canadian Medical Association Journal*, 174(4), 461-466.
- Leprout, R., Copinschi, G., Buxton, O., & Cauter, E. V. (1997). Sleep loss results in an elevation of cortisol levels the next evening. *Sleep*, 20, 865-870.
- Leserman, J., Jackson, E. D., Petitto, J. M., Golden, R. N., Silva, S. G., Perkins, D. O., et al. (1999). Progression to AIDS: The effects of stress, depressive symptoms, and social support. *Psychosomatic Medicine*, 61, 828-833.
- Levesque, L., Cossette, S. & Laurin, L. (1995). A multidimensional examination of the psychological and social well-being of caregivers of a demented relative. *Research on Aging*, 17, 332-360.
- Lichstein, K. L., Riedel, B. W., & Grieve, R. (1994). Fair tests of clinical trials: A treatment implementation model. *Advances in Behaviour Research and Therapy*, 16, 1-29
- Lieberman, M. A., Fisher, L. (2001). The Effects of Nursing Home Placement of Family caregivers of patients with Alzheimer's Disease. *The Gerontologist*, 41(6), 819-826.
- Locke, S. E., Bernard, J. R., Zachariae, R., Francine, M, Tollins, K., Covino, N. A., & Danforth, D. (1994). Effect of hypnotic suggestion on the delayed-type

- hypersensitivity response. *Journal of the American Medical Association*, 272, 47-52.
- Long, B. C., Haney, C. J. (1988). Long-term follow-up of stressed working women: A comparison of aerobic exercise and progressive relaxation. *Journal of Sport & Exercise Psychology*, *10*(4), 461-470.
- Lutgendorf, S. K. & Costanzo, E.S. (2003). Psychoneuroimmunology and health psychology: An integrative model. *Brain, Behavior, and Immunity*, *17*, 225-232.
- Lutgendorf, S. K., Antoni, M. H., Ironson, G., Klimas, N., McCabe, P., Cleven, K., et al., (1997). Cognitive-behavioral stress management decreases dysphoric mood and herpes simplex virus-type 2 antibody titers in symptomatic gay men. *Journal of Clinical and Consulting Psychology*, *65*, 31-43.
- Lutgendorf, S. K., Antoni, M. H., Ironson, G., Starr, K., Costello, N., Zuckerman, M., et al., (1998). Changes in cognitive coping skills and social support during cognitive behavioral stress management intervention and distress outcomes on symptomatic human immunodeficiency virus (HIV)-seropositive gay men. *Psychosomatic Medicine*, *60*, 204-214.
- Lutgendorf, S. K., Antoni, M. H., Kumar, M., & Schneiderman, N. (1994). Changes in cognitive coping strategies predict EBV-antibody titre change following a stressor disclosure induction. *Journal of Psychosomatic Research*, *38*, 63-78.
- Lutgendorf, S. K., Garand, L., Buckwalter, K. C., Reimer, T. T., Hong, S. Y., Lubaroff, D. M. (1999). Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. *Journal of Gerontology: Series A: Biological Sciences * Medical Sciences*, *54A*(9), M434-M439.

- Lutgendorf, S. K., Vitaliano, P. P., Tripp-Reimer, T., Harvey, J. H., & Lubaroff, D. M. (1999). Sense of coherence moderates the relationship between life stress and natural killer cell activity in healthy older adults. *Psychology and Aging, 14*, 552-563.
- Madden, K. S. (2003). Catecholamines, sympathetic innervation, and immunity. *Brain, Behavior, and Immunity 17*, S5-S10.
- Maddi, S. R., & Kobasa, S. C. (1984). *The hardy executive: Health under stress*. Homewood, IL: Dow-Jones Irwin.
- Maddi, S.R. (1990). Issues and Interventions in Stress Mastery. In *Personality and Disease: Wiley series on health psychology/behavioral medicine* (pp. 121-154). Friedman, H.S. (Ed.). Oxford: John Wiley & Sons.
- Maddi, S.R. (1997). Personal Views Survey-II: A measure of dispositional hardiness. In C. P. Zalaquett & R. J. Woods (Eds.), *Evaluating Stress: A book of resources*, New York: University Press.
- Maddi, S.R. (1999). Comments on Trends in Hardiness Research and Theorizing. *Consulting Psychology Journal: Practice and Research, Spring*, 67-71.
- Maddi, S.R. (1999). The Personality Construct of Hardiness: I. Effects on Experiencing, Coping, and Strain. *Consulting Psychology Journal: Practice and Research, Spring*, 83-94.
- Maddi, S.R. (2004). Hardiness: An operationalization of existential courage. *Journal of Humanistic Psychology, 44*(3), 279-298.
- Maddi, S.R., Hess, M.J.(1992). Personality Hardiness and Success in Basketball. *International Journal of Sport Psychology, 23*, 360-368.

- Maddi, S.R., Hightower, M. (1999). Hardiness and Optimism as Expressed in Coping Patterns. *Consulting Psychology Journal: Practice and Research*, Spring, 95-105.
- Maddi, S.R., Khoshaba, D.M.(1994). Hardiness and Mental Health. *Journal of Personality Assessment*, 63(2), 265-274.
- Maddi, S.R., Khoshaba, D.M.(1999). Early Experiences in Hardiness Development. *Consulting Psychology Journal: Practice and Research*, Spring, 106-116.
- Maddi, S.R., Khoshaba, D.M.(1999). The Hardy Organization: Success by Turning Change to Advantage *Consulting Psychology Journal: Practice and Research*, Spring, 117-124.
- Maddi, S.R., Khoshaba, D.M., Persico, M., Lu, J., Harvey, R., & Bleecker, F. (2002). The Personality Construct of Hardiness: II. Relationships with Comprehensive Tests of Personality and Psychopathology. *Journal of Research in Personality*, 36, 72-85.
- Maddi, S.R., Wadhwa, P., Haier, R.J. (1996). Relationship of Hardiness to Alcohol and Drug Use in Adolescents. *American Journal of Drug and Alcohol Abuse*, 22(2), 247-257.
- Maes, M., Bosmans, E., De Jongh, T., Kenis, G., Vandoolaeghe, E., & Neels, H. (1995). Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine*, 9, 853-858.
- Maes, M., DeVos, N., Wauters, A., Demedts, P., VandeWoude, M., Neels, H., Bosmans, E. Altamura, A., Lin, A., Song, C., Vandenbroucke, M., & Sharpe, S. (1999). Inflammatory markers in younger vs, elderly normal volunteers and in patients with Alzheimer's disease. *Journal of Psychiatric Research*, 33, 397-405.

- Maes, M., Lin, A., Delmeire, L., Van Gastel, A., Kenis, G., De Jongh, T., & Bosmans, E. (1999). Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. *Biological Psychiatry*, 45, 833-839.
- Maes, M., Song, C., Lin, A., De Jongh, R., Van Gastel, A., Kenis, G., Bosmans, E., De Meester, I., Benoy, L., Neels, H., Demedts, P., Janca, A., Scharpe, S., & Smith, R. S. (1998). The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine*, 10, 313-318.
- Mahoney, D. F., Jones, R. N., Coon, D. W., Mendelsohn, A. B., Gitlin, L. N., & Ory, M. (2003). The caregiver vigilance scale: Application and validation in the resources for enhancing Alzheimer's caregiver health (REACH) project. *American Journal of Alzheimer's Disease and other Dementias*, 18(1), 39-48.
- Maier, S. F. (2003). Bi-directional immune-brain communication: Implications for understanding stress, pain, and cognition. *Brain, Behavior, and Immunity*, 17, 69-85.
- Maier, S. F., & Watkins, L. R. (1998). Cytokines for Psychologists: Implications of Bidirectional Immune-to-Brain Communication for Understanding Behavior, Mood, and Cognition. *Psychological Review*, 105(1), 83-107.
- Maier, S. F., & Watkins, L. R. (2003). Immune-to-central nervous system communication and its role in modulating pain and cognition: Implications for cancer and cancer treatment. *Brain, Behavior, and Immunity*, 17, S125-S131.

- Maier, S. F., Groehler, L. E., Fleshner, M., & Watkins, L. R. (1998). The Role of the vagus nerve in cytokine-to-brain communication. *Annals of the New York Academy of Sciences*, 840, 289-300.
- Malarkey, W. B., Kiecolt-Glaser, J. K., Pearl, D., & Glaser, R. (1994). Hostile behavior during marital conflict affects pituitary and adrenal hormones. *Psychosomatic Medicine*, 56, 41-51.
- Malarkey, W.B., Wu, H., Cacioppo, J.T., Malarkey, K.L., Poehlmann, K.M., Glaser, R., & Kiecolt-Glaser, J. K. (1996). Chronic stress down regulates growth hormone gene expression in peripheral blood mononuclear cells of older adults. *Endocrine*, 5, 33-39.
- Marriott, A., Donaldson, C., Tarrier, N., & Burns, A. (2000). Effectiveness of cognitive—behavioural family intervention in reducing the burden of care in carers of patients with Alzheimer's disease. *British Journal of Psychiatry*, 176, 557-562
- Marsland, A. L., Cohen, S., Rabin, B. S., & Manuck, S. B. (2001). Associations between stress, trait affective affect, acute immune reactivity, and antibody response to hepatitis B injection in healthy young adults. *Health Psychology*, 20, 4-11.
- Marucha, P.T., Kiecolt-Glaser, J.K., & Favagehi, M. (1998). Mucosal wound healing is impaired by examination stress. *Psychosomatic Medicine*, 60, 362-365.
- Maxwell, S.E. (1980). Pairwise multiple comparisons in repeated measures designs. *Journal of Educational Statistics*, 5, 269-287.

- McCann, J. J. (1991). *Effects of stress on spousal caregivers psychological health and cellular immunity*. Unpublished doctoral dissertation, Rush University College of Nursing, Chicago.
- McCubbin, H., Larsen, A., & Olsen, D. (1981). *F-COPES* (Family Crises Oriented Personal Evaluation Scales) (measurement instrument) St. Paul, MN: Family Social Science, University of Minnesota.
- McDade, T. W., Hawkey, L. C., Cacioppo, J. T. (2006). Psychosocial and behavioral predictors of inflammation in Middle-aged and older adults: The Chicago health, aging, and social relations study. *Psychosomatic Medicine*, 68(3), 376-384.
- McEwen, B. S. (1998). Protective and Damaging effects of stress mediators. *New England Journal of Medicine*, 338, 171-179.
- McGuire, L., Kiecolt-Glaser, J. K., & Glaser, R. (2002) Depressive Symptoms and Lymphocyte Proliferation in Older Adults. *Journal of Abnormal Psychology*. 111, 192-197.
- McKee, K. J., Whittick, J. E., Ballinger, B. B., Gillhooly, M. M., Gordon, D. S., Mutch, W. J., & Phillip, I. (1997). Coping in family supporters of elderly people with dementia. *British Journal of Clinical Psychology*, 36, 323-340.
- McNair, D. M., Lorr, M., & Droppleman, L. F. (1981). *The Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Service.
- Miller, A.H. (1998). Neuroendocrine and Immune System Interactions in Stress and Depression. *Psychoneuroendocrinology*, 21(2), 443-451.

- Miller, B., Townsend, A., Carpenter, E., Montgomery, R. V. J., Stull, D., & Young, R. (2001). Social Support and Caregiver Distress: A Replication Analysis. *Journal of Gerontology*, 56B(4), S249-S256.
- Miller, G. E., Cohen, S., Ritchey, A. K. (2002). Chronic Psychological Stress and the Regulation of Pro-Inflammatory Cytokines: A Glucocorticoid-Resistant Model. *Health Psychology*, 21(6), 531-541.
- Mills, P. J., Dimsdale, J. E., Ziegler, M. G., Patterson, T. L. (2004). Vulnerable caregivers of Alzheimer disease patients have a deficit in β_2 -adrenergic receptor sensitivity and density. *American Association for Geriatric Psychiatry*, 12(3), 281-286.
- Miltiades, H.B., Pruchno, R. (2002). The Effect of Religious Coping on Caregiving Appraisals of Mothers of Adults with Developmental Disabilities. *The Gerontologist*, 42(1), 82-91.
- Mittleman, N.S., Roth, D. L., Coon, D. W., & Haley, W. E. (2004). Sustained benefit of supportive intervention for depressive symptoms in caregivers of patients with Alzheimer's Disease. *American Journal of Psychiatry*, 161, 850-856.
- Miyazaki, T., Ishikawa, T., Iimori, H., Miki, A., Wenner, M., Fukunishi, I., & Kawamura, N. (2003). Relationship between perceived social support and immune function. *Stress and Health*, 19(3), 3-7.
- Mohide, E.A., Pringle, D. M., Streiner, D. L., Gilbert, J. R. et al. (1990). A randomized trial of family caregiver support in the home management of dementia. *Journal of the American Geriatrics Society*, 38(4), 446-454.

- Moos, R. H. (1988). *Coping Response Inventory Manual* Palo Alto, CA: Stanford University Medical Center and Department of Veterans Affairs.
- Morag, M., Morag, A., Teichenberg, A., Lerer, B., & Yirmiya, R. (1999). Psychological variables as predictors of rubella antibody titers and fatigue- A prospective, double blind study. *Journal of Psychiatric Research*, 33, 389-395.
- Morgan, L.G. (1998). Psychoneuroimmunology: the Placebo Effect and Chiropractic. *Journal of Manipulative and Physiological Therapies*, 21(7), 484-491.
- Moynihan, J. A. (2003). Mechanisms of stress-induced modulation of immunity. *Brain, Behavior, and Immunity*, 17, S11-S16.
- Muller, H.K., Lugg, D.J., & Quinn, D. (1995). Cell mediated immunity in Antarctic winter personnel: 1984-1992. *Immunology and Cell Biology*, 73, 316-320.
- Navaie-Waliser, M., Feldman, P.H., Gould, D.A., Levine, C., Kuerbis, A.N., & Donelan, K. (2001). The Experiences and Challenges of Informal Caregivers: Common Themes and Differences among Whites, Blacks, and Hispanics. *The Gerontologist*, 41(6), 733-741.
- Neundorfer, M. M. (1991). Coping and mental health outcomes in spouse caregivers of persons with dementia. *Nursing Research*, 40, 260-265.
- Nyenhuis, D.L., Yamamoto, C., Luchetta, T., Terrien, A., Parmentier, A. (1999). Adult and geriatric normative data and validation of the profile of mood states. *Journal of Clinical Psychology*, 55 (1), 79-86.
- O'Connor, K.A., Holguin, A., Hansen, M. K., Maier, S. F., Watkins, L. R. (2004). A method for measuring multiple cytokines from small samples. *Brain, Behavior, and Immunity*, 18, 274-280.

- O'Leary, A., Brown, S., & Suarez-Al-Adam, M. (1997). Stress and Immune Function. In *Clinical Disorders and Stressful Life Events*. (pp. 181-215). T.W. Miller (Ed.)
Madison: International University Press.
- O'Leary, V., & Ickovics, J. (1995). Resilience and thriving in response to challenge: An opportunity for a paradigm shift in women's health. *Women's Health: Research on Gender, Behavior, and Policy, I*, 121-142.
- Opp, M. (2004). Cytokines and sleep: the first hundred years. *Brain, Behavior, and Immunity, 18*, 295-297.
- Orts, K., Sheridan, J. F., Robinson-Whelen, S., Glaser, R., Malarkey, W. B., & Kiecolt-Glaser, J. K. (1995). The reliability and validity of a structured interview for the assessment of infectious illness symptoms. *Journal of Behavioral Medicine, 18*, 517-529
- Papanicolaou, D. A., Wilder, R. L., Manolagas, S. C., & Chrousos, G. P. (1998). The pathophysiologic roles of interleukin-6 in human disease. *Annals of Internal Medicine, 128*, 127-137.
- Pariante, C.M., Carpinello, B., Orru, M.G., Sitzia, R., Piras, A., Farci, A.M., Del Giacco, G.S., Piludu, G., & Miller, A.H. (1997). Chronic Caregiving Stress alters Peripheral Blood Immune Parameters: The role of age and the severity of stress. *Psychotherapy and Psychosomatics, 66*, 199-207.
- Paterson, R.J., Neufeld, R. W. (1989). The Stress response and Parameters of Stressful Situations. In *Advances in the Investigation of Psychological Stress* (pp. 7-42). R.W.J. Neufeld (Ed.). New York: John Wiley & Sons.

- Patterson, T. L., & Grant, I. (2003). Interventions for caregiving in dementia: physical outcomes. *Current Opinions in Psychiatry*, 16 (6), 629-633.
- Pearlin, L. I., Millan, J. T., Semple, S. J., & Skaff, M. M. (1990). Caregiving and the stress process: An overview of concepts and their measures. *The Gerontologist*, 30, 583-595.
- Pennebaker, J. W., Kiecolt-Glaser, J. K., & Glaser, R. (1988). Disclosure of traumas and immune function: Health implications for psychotherapy. *Journal of Consulting and Clinical Psychology*, 56, 239-245.
- Peterson, R., & Headen, S. (Eds.) (1984). *Profile of Mood States*. (Vol. 1). Kansas City, MO: Westport Publishers.
- Petrie, K. J., Booth, R. J., Pennebaker, J. W., Davison, K. P., & Thomas, M. G. (1995). Disclosure of trauma and immune response to a hepatitis B vaccination program. *Journal of Consulting and Clinical Psychology*, 63, 787-792.
- Pett, M.A., Caserta, M. S., Hutton, A. P., & Lund, D. A. (1988). Intergenerational conflict: Middle-aged women caring for demented older relatives. *American Journal of Orthopsychiatry*, 58, 405-417.
- Pierpaoli, W., Lesnikov, V. (1997). Theoretical Considerations on the nature of the Pineal 'Ageing Clock'. *Gerontology*, 43, 20-25.
- Pinquart, M., Sorenson, S. (2003). Differences Between Caregivers and Noncaregivers in Psychological Health and Physical Health: A Meta-Analysis. *Psychology and Aging*, 18(2), 250-267.
- Pollock, S. E., Duffy, M. E. (1990). The Health Related Hardiness Scale: Development and Psychometric analysis. *Nursing Research*, 39, 218-222.

- Pratt, C., Schmall, V., Wright, S., & Cleland, M. (1985). Burden and coping strategies of caregivers to Alzheimer patients. *Family Relations*, 34, 27-33.
- Pusey, H., & Richards, D. (2001). A systematic review of the effectiveness of psychosocial interventions for carers of people with dementia. *Aging and Mental Health*, 5(2), 107-119.
- Rabin, B. S. (1999). *Stress, immune function, and health: the connection*. New York: Wiley-Liss & Sons.
- Radloff, L.S. (1977). The CES-D scale: A self-report depression scale for research in the general population, *Applied Psychological Measurement*, 1, 385-401.
- Redinbaugh, E. M., MacCallum, R. C., & Kiecolt-Glaser, J. K. (1995). Recurrent syndromal depression in caregivers. *Psychology and Aging*, 10, 358-368.
- Reed, G. M., Kemeny, M. E., Taylor, S. E., & Visscher, B. R. (1999). Negative HIV-specific expectancies and AIDS-related bereavement as predictors of symptom onset in asymptomatic HIV-positive gay men. *Health Psychology*, 18, 354-363.
- Reese, D., Gross, A. M., Smalley, D. L., & Messer, S. C. (1994). Caregivers of Alzheimer disease and stroke patients: Immunological and psychological considerations. *Gerontologist*, 34, 534-540.
- Reinherz, E. L., & Schlossman, S. F. (1980). Current concepts in immunology: Regulation of the immune response-inducer and suppressor T-lymphocyte subsets in human beings. *New England Journal of Medicine*, 303, 370-373.
- Reitan, R., & Wolfson, D. (1992). *Neuroanatomy and Neuropathology: A Clinical Guide for Neuropsychologists*. (2nd ed.). Tucson, AZ:Neuropsychology Press.

- Reuben, D. B., Ferrucci, L., Wallace, R., Tracy, R. P., Corti, M. C., Heimovitz, H., & Harris. (2000). The prognostic value of serum albumin in healthy older persons with low and high serum interleukin-6 (IL-6) levels. *Journal of the American Geriatric Society*, 48, 1404-1407.
- Richardson, J. L., Shelton, D. R., Kralia, M., & Levine, A. M. (1990). The Effect of compliance with treatment on survival among patients with hematologic malignancies. *Journal of Clinical Oncology*, 8 (2), 356-364.
- Rivest, S. (1999). What is the cellular source of prostaglandins in the brain in response to sytemic inflammation: Facts and controversies. *Molecular Psychiatry*, 4, 501-508.
- Roberts, J., Browne, G., Milne, C., Spooner, L., Gafni, A., Drummond-Young, M., LeGris, J., Watt, S., LeClair, K., Beaumont, L., & Roberts, J. (1999). Problem-Solving Counseling for Caregivers of the Cognitively Impaired: Effective for Whom? *Nursing Research*, 48(3), 162-172.
- Robinson-Whelen, S., Kiecolt-Glaser, J. K., & Glaser, R. (2000). Effects of chronic stress on immune function and health in the elderly. In *Behavior, Health, and Aging* (pp. 69-82). Manuck, S. B. & Jennings, R. (Eds.) Mahwah, New Jersey: Lawrence Erlbaum Associates, Publishers.
- Robinson-Whelen, S., Tada, Y., MacCallum, R. C., McGuire, L., & Kiecolt-Glaser, J. K. (2001). Long-term caregiving: What happens when it ends? *Journal of Abnormal Psychology*, 110, 573-584.
- Rockefeller, J. D. (1991). A call for action: The Pepper Commission's blueprint for healthcare reform . *Journal of the American Medical Association*, 265, 2507-2510.

- Roitt, I., Brostoff, J., & Male, D. (1993). *Immunology*, 3rd Edition. London, United Kingdom: Mosby Publishers.
- Rojas, L., Padgett, D. A., Sheridan, J. F., & Marucha, P. T. (2002). Stress-induced susceptibility to bacterial infection during cutaneous wound healing. *Brain, Behavior, and Immunity*, 16, 78-84.
- Russell, R. (2001). In sickness and in health: A qualitative study of elderly men who care for wives with dementia. *Journal of Aging Studies*, 15, 351-367.]
- Saad, K., Hartman, J., Ballard, C., Kurian, M., Graham, C., & Wilcox, G. (1995). Coping by carers of dementia sufferers. *Age and Ageing*, 24, 495-498.
- Sapolsky, R. M., Krey, L. C., McEwen, B. S. (1986). The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. *Endocrine Review*, 7, 284-287.
- Schedlowski, M., Falk, A., Rohne, A., Wagner, T.O.F., Jacobs, R., Tewes, U., & Schmidt, R.E. (1993). Catecholamines induce alterations of distribution and activity of human natural killer (NK) cells. *Journal of Clinical Immunology*, 13, 34-351.
- Schneiderman, N., Antoni, M., Ironson, G., Klimas, N., Lapierre, A., Kumar, M., et al., (1994). HIA-1 immunity, and behavior. In R. Glaser & J. K. Kiecolt-Glaser (Eds.), *Handbook of human stress and immunity*, (pp. 267-300). San Diego, CA: Academic Press.
- Schneiderman, N., Antoni, M., Saab, P. G., & Ironson, G., (2001). Health Psychology: Psychosocial and biobehavioral aspects of chronic disease management. *Annual Review of Psychology*, 52, 555-580.

- Schulz, R., & Beach, S. R. (1999) Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA*, 282, 2215-9.
- Schulz, R., & Martire, L.M. (2004). Family caregiving of persons with dementia: Prevalence, health effects, and support strategies. *American Association for Geriatric Psychiatry*, 12(3), 240-249.
- Schulz, R., & O'Brien, A. (1994). Alzheimer's disease caregiving: An overview. *Seminars in Speech and Language*, 15, 185-193.
- Schulz, R., & Patterson, T. L. (2004). Caregiving in geriatric psychiatry. *American Association for Geriatric Psychiatry*, 12(3), 234-237.
- Schulz, R., O'Brien, A., Czaja, S., Ory, M., Norris, R., Martire, L.M., Belle, H. S., Burgio, L. Gitlin, L., Coon, D., Burns, R., Gallagher-Thompson, D., & Stevens, A. (2002). Dementia Caregiver Intervention Research: In Search of Clinical Significance. *Gerontologist*, 42(5), 589 - 602.
- Schulz, R., O'Brien, A., Bookwala, J., & Fleissner, K. (1995). Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist*, 35, 771-91.
- Schulz, R., Visintainer, P., & Williamson, G.M. (1990). Psychiatric and physical morbidity effects of caregiving. *Journal of Gerontology: Psychological Sciences*, 45, P181-191.
- Segerstrom, S. C. (2000). Personality and the Immune System: Models, Methods, and Mechanisms. *Annals of Behavioral Medicine*, 22, 180-190.
- Segerstrom, S. C. (2001). Optimism, goal conflict, and stressor-related immune change. *Journal of Behavioral Medicine*, 24(5), 441-467.

- Segerstrom, S. C., Casteneda, J. O., & Spencer, T. E. (2003). Optimism effects on cellular immunity: testing the affective and persistence models. *Personality and Individual Differences, 35*(7), 1615-1624.
- Segerstrom, S. C., Taylor, S. E., Kemeny, M. E., & Fahey, J. L. (1998). Optimism is associated with mood, coping, and immune change in response to stress. *Journal of Personality and Social Psychology, 74*, 1646-1655.
- Selye, H. (Ed.), (1980). *Selye's Guide to Stress Research*. Van Nostrand Reinhold Company: San Francisco.
- Shapiro, D.H., Schwartz, C.E., & Astin, J.A. (1996). Controlling Ourselves, Controlling our World: Psychology's Role in Understanding Positive and Negative Consequences of Seeking and Gaining Control. *American Psychologist, 51* (12), 1213-1230.
- Shaw, W. S., Patterson, T. L., Semple, S., Dimsdale, J. E., Ziegler, M. G., & Grant, I. (2003). Emotional expressiveness, hostility and blood pressure in a longitudinal cohort of Alzheimer caregivers. *Journal of Psychosomatic Research, 54*, 293-302.
- Shaw, William S.; Patterson, Thomas L.; Ziegler, Michael G.(1999). Accelerated risk of hypertensive blood pressure recordings among Alzheimer caregivers. *Journal of Psychosomatic Research, 46*(3), 215-227.
- Sheridan, J. (2003). The HPA axis, SNS, and immunity: A commentary. *Brain, Behavior, and Immunity, 17*, S17.
- Shi, Y., Devadas, S., Greenelch, K. M., Yin, D., Mufson, R. A., Zhou, J. (2003). Stressed to death: Implication of lymphocyte apoptosis for psychoneuroimmunology. *Brain, Behavior, and Immunity, 17*, S18-S26.

- Sjögren, E., Leanderson, P., Kristenson, M. & Ernerudh, E. (2006). Interleukin-6 levels in relation to psychosocial factors: Studies on serum, saliva, and in vitro production by blood mononuclear cells. *Brain, Behavior, and Immunity*, 20, 270-278.
- Smith, C. J., Emsley, H., Gavin, C. M., Georgiou, R. F., Vail, A., Barberan, E. M., del Zoppo, G. J., Hallenbeck, J. M., Rothwell, N. J., Hopkins, S. J., & Tyrrell, P. J. (2004). Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity, and long-term outcome. *BioMed Central Neurology*, 4(2), 1-16.
- Smyth, J. M., Soefer, M. H., Hurewitz, A. (1999). The effect of tape-recorded relaxation training on well-being, symptoms, and peak expiratory flow rate in adult asthmatics: A pilot study. *Psychology & Health*, 14(3), 487-501.
- Smyth, K.A., Milidonis, M.K. (1999). The Relationship between Normative Beliefs about Help Seeking and the Experience of Caregiving in Alzheimer's Disease. *The Journal of Applied Gerontology*, 18(2), 222-238.
- Solomon, G. F., Segerstrom, S. C., Grohr, P., Kemeny, M. E., & Fahey, J. (1997). Shaking up immunity: Psychological and immunological changes after a natural disaster. *Psychosomatic Medicine*, 59, 114-127.
- Solomon, G.F. & Moos, R.H. (1964). Emotions, Immunity, and Disease: A Speculative Theoretical Integration. *Archives of General Psychiatry*, 11, 657-674.
- Solomon, G.F. (1993). Whither Psychoneuroimmunology? A new era of immunology, of Psychosomatic Medicine, and of Neuroscience. *Brain, Behavior, and Immunity*, 7, 356-366.

- Sorenson, S., Pinquart, M., & Duberstein, P. (2002). How Effective are Interventions with Caregivers? An Updated Meta-Analysis. *The Gerontologist*, 42(3), 346-372.
- Spiegel, D., Bloom, J. R., & Yalom, I. (1981). Group support for patients with metastatic cancer: A randomized prospective outcome study. *Archives of General Psychiatry*, 38 (5), 527-533.
- Spiegel, D., Bloom, J. R., Kraemer, H. C., & Gottheil, E. (1989). Effects of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet*, 334 (8668), 888-892.
- Stanford University School of Medicine, (2000). *Coping with Caregiving*.
<http://www-med.stanford.edu/oac/>.
- Steffen, A.M., McKibbin, C., Zeiss, A.M., Gallagher-Thompson, D., Bandura, A. (2002). The Revised Scales for Caregiver Self-Efficacy: Reliability and Validity Studies. *Journal of Gerontology*, 57 B(1), 74-86.
- Sternberg, E. M., Chrousos, G. P., Wilder, R. L., & Gold, P. W. (1992). The stress response and the regulation of inflammatory disease. *Annals of Internal Medicine*, 117, 854-866.
- Stevens, A., & Hochhalter, A. (2006). Personal Communication.
- Stolley, J.M., Buckwalter, K.C., & Koenig, H.G. (1999). Prayer and religious coping for caregivers of persons with Alzheimer's disease and related disorders. *American Journal of Alzheimer's Disease*, 14(3), 181-191.
- Stommel, M., Collins, C.E., Given, B.A., Given, C.W. (1999). Correlates of Community Service among Family Caregivers. *The Journal of Applied Gerontology*, 18(2), 145-161.

- Stone, A. A., Neale, J. M., Cox, D. S., Napoli, A., Valdimarsdottir, H., & Kennedy-Moore, E. (1994). Daily events are associated with a secretory immune response to an oral antigen in men. *Health Psychology, 13*, 440-446.
- Stout, J.C., Bondi, M.W., Jernigan, T.L., Archibald, S.L., Delis, D.C., & Salmon, D.P. (1999). Regional Cerebral Volume Loss Associated with Verbal Learning and Memory in Dementia of the Alzheimer's Type. *Neuropsychology, 13* (2), 188-197.
- Stowell, J. R., Kiecolt-Glaser, J. K., & Glaser, R. (2001). Perceived stress and cellular immunity: When coping counts. *Journal of Behavioral Medicine, 24*, 323-340.
- Stuckey, J.C., Neundorfer, M.M., Smyth, K.A. (1996). Burden and Well-Being: The Same Coin or Related Currency? *The Gerontologist, 36*(5), 686-693.
- Suarez, E.C. (2003). Plasma interleukin-6 is associated with psychological coronary risk factors: Moderation by use of multivitamin supplements. *Brain, Behavior, and Immunity, 17*, 296-303.
- Sutcliffe, C. & Larer, S. (1988). Counselling carers of the elderly at home: A preliminary study. *British Journal of Clinical Psychology, 27*, 177-178.
- Taafé, D. F., Harris, T. B., Ferrucci, L., Rowe, J., & Seeman, T. E. (2000). Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur Studies of Successful Aging. *Journals of Gerontology: Biological Sciences and Medical Sciences, 55A*, M709-M715.
- Tarlow, B. J., Wisniexski, S. R., Belle, S. H., Rubert, M., Ory, M. G., & Gallagher-Thompson, D. (2004). Positive aspects of caregiving: Contributions of the

- REACH project to the development of new measures for Alzheimer's caregiving. *Research on Aging*, 26(4), 429-453.
- Teri, L., Truax, P., Logson, R., Uomoto, J., Zarit, S., Vitaliano, P. P. (1992). Assessment of behavioral problems in dementia: The Revised Memory and Behavior Problems Checklist. *Psychology and Aging*, 7, 622-631.
- Tsigos, C., Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors, and stress. *Journal of Psychosomatic Research*, 53(4), 865-871.
- Uchino, B.N., Kiecolt-Glaser, J.K., & Cacioppo, J.T.(1996). The Relationship between Social Support and Physiological Processes: A Review with Emphasis on Underlying Mechanisms and Implications for Health. *Psychological Bulletin*, 119(3), 488-531.
- United States Administration on Aging (AOA) (1998a). *Aging Research & Training News*, 21 (4). Silver Springs, MD: Business Publishers, Inc.
- United States Administration on Aging (AOA) (1998b). *Aging Research & Training News:Special Report*. Silver Springs, MD: Business Publishers, Inc.
- United States Administration on Aging (AOA) (1999a). *Aging Research & Training News*, Silver Springs, MD: Business Publishers, Inc.
- United States Administration on Aging (AOA) (1999b). *Older Americans Report: Slants and Trends*. Silver Springs, MD: Business Publishers, Inc.
- Validimarsdottir, H. B., & Bovbjerg, D. H. (1997). Positive and negative mood: Association with natural killer cell activity. *Psychology and Health*, 12, 319-327.

- Van Rood, Y.R., Bogaards, M., Goulmy, E., VanHouwelingen, H. C. (1993). The effects of stress and relaxation on the in vitro immune response in man: A meta-analytic study. *Journal of Behavioral Medicine*, 16 (2), 163-181.
- Vedhara, K., Addy, L., & Wharton, L. (2000). The role of social support as a moderator of the acute stress response: In situ versus empirically-derived associations. *Psychology and Health*, 15, 297-307.
- Vedhara, K., Bennett, P. D., Clark, S., Lightman, S. L., Shaw, S., Perks, P., Hunt, M. A., Philip, J. M. D., Tallon, D., Murphy, P. J., Jones, R. W., Wilcock, G. K., & Shanks, N. M. (2003). Enhancement of antibody responses to influenza vaccination in the elderly following a cognitive-behavioural stress management intervention. *Psychotherapy and Psychosomatics*, 72, 245-252.
- Vedhara, K., Cox, N.K., Wilcock, G.K., Perks, P., Hunt, M., Anderson, S., Lightman, S.L., & Shanks, N. M. (1999). Chronic stress in elderly caregivers of dementia patients and antibody response to influenza vaccination. *Lancet*, 353, 627-631.
- Vedhara, K., Fox, J. D., & Wang, E. C. Y. (1999). The measurement of stress-related immune dysfunction in psychoneuroimmunology. *Neuroscience and Behavioral Reviews*, 23(5), 699-715.
- Vedhara, K., Hyde, J., Gilchrist, I. D., Tytherleigh, M., & Plummer, S. (2000). Acute stress, memory, attention and cortisol. *Psychoneuroendocrinology*, 25(6), 535-549.
- Vedhara, K., McDermott, M. P., Evans, T. G., Treanor, J. T., Plummer, S., Tallon, D., Cruttenden, K. A., & Schifitto, G. (2002). Chronic stress in elderly caregivers:

- Psychological, endocrine, and immune implications. *Journal of Psychosomatic Research*, 53(6), 1153-1161.
- Vedhara, K., Shanks, N., Anderson, S., & Lightman, S. (2000). The Role of Stressors and Psychosocial Variables in the Stress Process: A Study of Chronic Caregiver Stress. *Psychosomatic Medicine*, 62(3), 374-385.
- Veldhuis, J. D., & Iranmanesh, A. (1996). Physiological regulation of the human growth hormone (GH)-insulin-like growth factor type I (IGF-I) axis : Predominant effect of age, obesity, gonadal function, and sleep. *Sleep*, 19, S221-S224.
- Verma, S., Nakaoke, R., Dohgu, S. & Banks, W. A. (2006). Release of cytokines by brain endothelial cells: A polarized response to lipopolysaccharide. *Brain, Behavior, and Immunity*, 20 (5), 449-455.
- Vetter, P. H., Krauss, S., Steiner, O., Kropp, P., Muller, W. D., Moises, H. W., & Koller, O. (1999). Vascular Dementia versus Dementia of the Alzheimer's Type: Do they have differential effects of caregiver burden? *Journal of Gerontology*, 54B(2), 893-898.
- Vitaliano, P. P., Russo, J., Carr, J. R., Young, H. M., Maiuro, R. D., & Becker, J. (1985). The Ways of Coping Checklist: Revision and psychometric properties. *Multivariate Behavioral Research*, 20,3-26.
- Vitaliano, P. P., Scanlan, J. M., Ochs, H.D., Syrjala, K., Siegler, I.C., & Snyder, E.A. (1998). Psychosocial stress moderates the relationship of cancer history with natural killer cell activity. *Annals of Behavioral Medicine*, 20, 199-208.

- Vitaliano, P. P., Russo, J., Young, H., Teri, L., and Maiuro, R. D. (1991). Predictors of burden in spouse caregivers of Alzheimer's patients. *Research in Nursing and Health*, 20, 27-37.
- Vitaliano, P. P., Scanlan, J. M., Zhang, J., Savage, M. V., Hirsch, I. B., & Siegler, I. C. (2002). A Path Model of Chronic Stress, the Metabolic Syndrome, and Coronary Heart Disease. *Psychosomatic Medicine*, 64(3), 477-486.
- Volpato, S., Guralnik, J. M., Ferruci, L., Balfour, J., Chaves, P., Fried, L. P., & Harris, T. B. (2001). Cardiovascular disease, interleukin-6, and risk of mortality in older women: the women's health and aging study. *Circulation*, 103, 947-953.
- Von Kanel, R., Dimsdale, J. E., Mills, P., Ancoli-Israel, S., Patterson, T., Mausbach, B. T., & Grant, I. (2006). Effect of Alzheimer caregiver stress and age on frailty markers Interleukin-6, C-Reactive Protein, and D-Dimer. *Journal of Gerontology*, 61 (9), 963-969.
- Watkins, L. R., Maier, S. F., & Goehler, L. E. (1994). Immune activation: The role of proinflammatory cytokines in inflammation, illness responses, and pathological pain states. *Pain*, 63, 289-302.
- Watkins, L. R., & Maier, S. F. (2000). The pain of being sick: Implications of Immune-to-Brain Communication for Understanding Pain. *Annual Review of Psychology*, 51, 29-57.
- Watkins, L. R., Wiertelak, E. P., Goehler, L. E., Mooney-Heiberger, K., Martinex, J., Furness, L., Smith, K. P., Iadorola, M. J., & Maier, S. F. (1994). Neurocircuitry of illness-induced hyperalgesia. *Brain Research*, 639, 283-299.

- Webb, M. G. (1995). *The effect of progressive relaxation on anger, personal strain, bloodpressure, and heart rate in employed African-American women*. Dissertation Abstracts International: Section B: The Sciences & Engineering, Vol 55(10-B), 4325.
- Wiebe, D. J., & Williams, P. G. (1992). Hardiness and health: A social psychophysiological perspective on stress and adaptation. *Journal of Social and Clinical Psychology, 11*(3), 238-262.
- Wieler, P.G., Chiriboga, D.A., & Black, S.A. (1994). Comparison of Mental Status Tests: Implications for Alzheimer's Patients and Their Caregivers. *Journal of Gerontology, 49*(1), S44-S51.
- Wilcox, S., King, A.D., Vitaliano, P.P., & Brassington, G.S. (2000). Anger Expression and natural Killer Cell Activity in Family Caregivers Participating in a Physical Activity Trial. *Journal of Health Psychology, 5*(4), 431-440.
- Wilkins, S. S., Castle, S., Heck, E., Tanzy, K., & Fahey, J. (1999). Immune function, mood, and perceived burden among caregivers participating in a psychoeducational intervention. *Psychiatric Services, 50*(6), 747-749.
- Wirtz, P. H., von Kanel, R., Schnorpfiel, P., Ehlert, U., Frey, K., & Fisher, J. E. (2003). Reduced glucocorticoids sensitivity of monocyte interleukin-6 production in male industrial employees who are vitally exhausted. *Psychosomatic Medicine, 65*, 672-678.
- Wisniewski, S.R., Belle, S.H., Coon, D.W., Marcus, S.M., Ory, M.G., Burgio, L.D., Burns, AR. (2003). The Resources for Enhancing Alzheimer's Caregiver Health

- (REACH): Project Design and Baseline Characteristics. *Psychology and Aging*, 18(3), 375-384.
- Wright, L. K. (1994). AD spousal caregivers: Longitudinal changes in health. *Journal of Gerontological Nursing*, 20, 30-48.
- Wu, H., Wang, J., Cacioppo, J.T., Glaser, R., Kiecolt-Glaser, J.K., & Malarkey, W. (1999). Chronic Stress Associated with Spousal Caregiving of Patients with Alzheimer's Dementia is associated with Downregulation of B-Lymphocyte GHmRNA. *Journal of Gerontology*, 54(4), 212-215.
- Yang, E. V., Bane, C., MacCallum, R. C., Kiecolt-Glaser, J. K., Malarkey, W. B., & Glaser, R. (2002). Modulation of matrix metalloproteinase expression by stress-related hormones. *Journal of Neuroimmunology*, 133, 144-150.
- Yang, E. V., Glaser, R. (2002). Stress-induced immunomodulation and the implications for health. *International Immunopharmacology*, 2, 315-324.
- Yehuda, R. (2003). Hypothalamic-pituitary-adrenal alterations in PTSD: Are they relevant to understanding cortisol alterations in cancer? *Brain, Behavior, and Immunity*, 17, S73-S83.
- Zarit, S. H; Anthony, C. R; & Boutselis, M. (1987). Interventions with care givers of dementia patients: Comparison of two approaches . *Psychology & Aging*, 2(3), 225-232.
- Zatura, A. J., Hoffman, J. M., Matt, K. S., Yocum, D., Potter, P. T., CastrO, W. L., & Roth, S. (1998). An examination of individual differences in the relationship between interpersonal stress and disease activity among women with rheumatoid arthritis. *Arthritis Care and Research*, 11, 271-279.

Zhang, J., Vitaliano, P. P., Lutgendorf, S. K., Scanlan, J. P., & Savage, M. V. (2001).

Sense of coherence buffers relationships of chronic stress and fasting glucose levels. *Journal of Behavioral Medicine*, 24(1), 33-55.

Zhou, D., Kusnecov, A. W., Shurin, M. R., DePaoli, M., & Rabin, B. S. (1993).

Exposure to physical and psychological stressors elevates plasma interleukin 6: Relationship to the activation of hypothalamic-pituitary-adrenal axis.

Endocrinology, 133, 2523-2530.

APPENDIX A

Glossary

Acute-phase response- a complex set of widespread changes throughout the entire organism that also function to combat infection and injury orchestrated by the proinflammatory cytokines; the global reaction to infection or injury. Specifically, they include Physiological responses (fever, increased slow-wave sleep, alterations in plasma ions, shifts in liver protein synthesis, increased levels of circulating white blood cells); Behavioral changes (hyperalgesia, reductions in activity, exploration, social interaction, aggression, and sexual behavior); Cognitive alterations (decreased attention, interference with some aspects of memory). May include activation of the HPA axis.

Allostasis: describes the body's ability to adapt to constantly changing environments; the ability to achieve stability through change.

Allostatic Load: Physical damage due to stress that occurs when the body is under chronic stress and in a constant state of SNS arousal.

Catecholamines: Epinephrine and norepinephrine. Released by the adrenal medulla as part of SAM axis activation as part of the classic stress response.

C-Reactive protein(CRP)- a protein whose concentration in serum increases rapidly during infection; known as an acute phase protein. Can bind to the C-protein of pneumococci. Promotes the binding of Complement.

Complement- a group of about 20 serum proteins whose overall function is the control of inflammation. Stimulates phagocytes to engulf bacteria. Cascade of ~11 plasma complement proteins (C) function to destroy target cell membranes, stimulate inflammation, attract phagocytes, and enhance phagocytosis.

Cytokines- Cytokine is simply a generic term for soluble molecules which mediate interactions between cells. Secreted by helper T-cells (see proinflammatory cytokines). The interferons (IFNs) and interleukins (IL) are two broad groups of cytokines.

ELISA-Enzyme-linked immunosorbant assay- the kits are used to measure levels of pro-inflammatory cytokines

Glucocorticoids: Responsible for the trafficking (redistribution) of lymphocytes and for the stress-enhancement of delayed-type hypersensitivity. Cortisol is a glucocorticoid.

Hematopoietic- pertaining to or effecting the formation of blood cells.

Hypothalamic-pituitary-adrenal (HPA) axis: When activated, part of the classic stress response which entails release of CRF, ACTH and glucocorticoids.

Inflammation: Localized tissue response to injury producing swelling, redness, heat, pain. Effects of inflammation include the temporary repair of injury, slowing the spread of pathogens, and mobilization of local, regional, and systemic defenses.

Interferons (IFNs): a group of mediators which increase the resistance of cells to viral infection, and act as cytokines. IFN γ is an important immunological mediator. Three major types of interferons are: Alpha– produced by leukocytes and attract/stimulate NK cells; Beta– secreted by fibroblasts causing slow inflammation ; Gamma – secreted by T cells and NK cells stimulate macrophage activity.

Interleukins (IL): a group of molecules involved in signaling between cells of the immune system.

Interleukin-6 (IL-6): a major circulating cytokine produced in response to inflammatory insult and infection and is a potent stimulus for production of hepatic (liver) acute phase proteins, induction of fever, and activation of the hypothalamic-pituitary-adrenal axis. IL-6 levels increase with age, possibly due to the loss of normally inhibiting sex steroids (estrogen, testosterone), is strongly implicated in processes involved in normal aging as well as in the pathogenesis of a number of age-related conditions. IL-6 is a pleiotropic cytokine that plays a crucial role in immune physiology and is tightly controlled by hormonal feedback mechanisms.

LPS- Lipopolysaccharide: a B-lymphocyte mitogen

Lymphocytes: There are three subtypes of lymphocytes: B-lymphocytes, produced in the bone marrow; T-lymphocytes, produced in the thymus; and the natural killer (NK) cell.

Lysis: dissolution, destruction or decomposition of cells by a specific lysine or agent.

Mediate: indirect; accomplished by the aid of an intervening medium.

Mediator: a substance released from the cells as the result of the interaction of antigen with antibody.

Mitogen: substances used in the laboratory that have the ability to stimulate lymphocyte proliferation or replication for large subsets of lymphocytes; analogous to a master key

Moderate(tor): something that alters or changes.

Phytohemagglutinin (PHA)-stimulates proliferation of T-cells

Pleiotropic- producing many effects in the phenotype.

Pleiotropy- the quality of a gene to manifest itself in a multiplicity of ways, i.e.. to produce effects in the phenotype.

Proinflammatory Cytokines: there are three cytokines known as pro-inflammatory cytokines : IL-6, IL-1 β and tumor necrosis factor alpha- TNF α . As a group, the proinflammatory cytokines have been implicated in the onset and course of a number of age-associated diseases, such as general frailty and functional decline, Alzheimer's disease, periodontal disease, osteoporosis, arthritis, type 2 diabetes, cardiovascular disease, as well as certain cancers. They are all directly associated in the manifestation of the symptoms of sickness as well, such as fever, inflammation, listlessness, and depressed appetite.

Psychoneuroimmunology (PNI): Essentially, the study of the effects of psychological stress and its effects on the immune system.

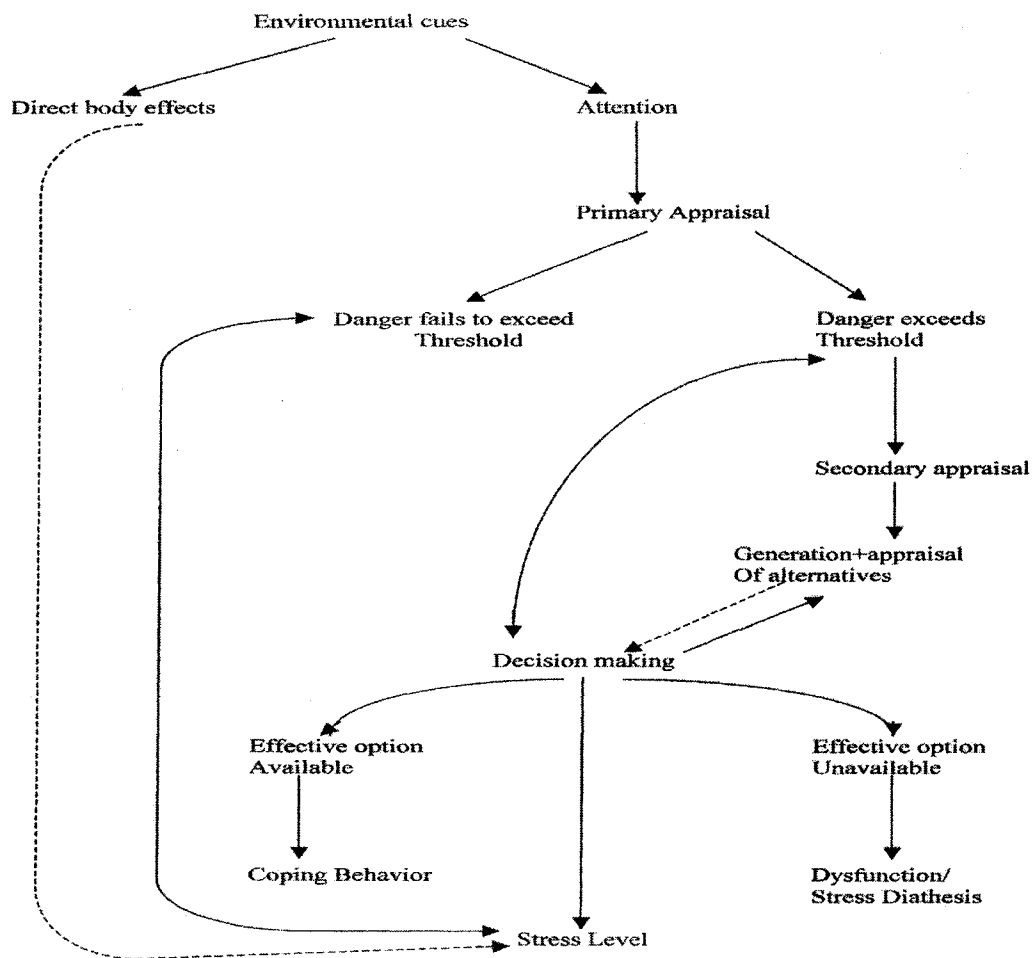
Reagents: substance(s) employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances.

Sympathetic-adrenal-medullary (SAM) axis: When activated, part of the classic stress response which entails release of plasma catecholamines.

Telomeres: DNA-protein complexes that cap chromosomal ends and promote chromosomal stability. Telomeres shorten with age in all replicating somatic cells that have been examined, and can serve as a biomarker of cell biological (vs. chronological) age.

APPENDIX B

Model of Stress



Schematic representation of Lazarus and Folkman's stimulus-appraisal-response stress coping model. Paterson & Neufeld (1989)

APPENDIX C

PVS III-R® Survey

Personal Views Survey-III-Revised

Please answer the following 18 questions to the best of your ability, and as honestly as possible. This is important for report accuracy. There are no right or wrong answers. You begin by responding to the demographic categories that appear below. Review each demographic category and place an X or a check mark next to the item within each demographic category that applies to you.

IMPORTANT: You are part of a research study; please DO NOT include your name, address, and phone number. Please include your true gender, age, race/ethnicity, education, industry, occupation, and living status or your test cannot be scored.

When you complete this demographic page, you are ready to take the PVS®III-R and on your way to enhancing your performance, leadership, and health. Please answer each question by circling the number that best describes your current views and life situation.

Age (16-90) How old are you? _____ (exact age please)

Gender: Male: _____; Female: _____

Education (place a check or x to the response that applies to you)

Less than high school: _____

High school: _____

Bachelor degree: _____

Trade School degree: _____

Associate degree: _____

Ph.D. or Psy.D.: _____

Nursing Degree: _____

Medical Doctor (this includes Dentists, Chiropractors, and Osteopathic): _____

Other: _____

Industry (place a check or x to the response that applies to you)

Army: _____; Navy: _____; Agricultural: _____; Building and Construction: _____

_____; Restaurant: _____; Hotel: _____; Academia: _____; Pharmaceutical: _____; Government: _____; Emergency

Protection: _____

_____; Nursing: _____; Mental Health Care: _____;

Medical: _____; Insurance: _____; Entertainment: _____;

Publishing: _____; Engineering: _____; Aerospace: _____;

Electronic: _____; Computer: _____; Legal: _____;

Other: _____ (please identify).

Living Status (place a check or x to the response that applies to you)

Single: _____

Married: _____

Divorced: _____

Remarried: _____

Unmarried but living w/sig. other: _____

Number of times you have taken this test: (place a check or x to the response that applies to you): First: _____ Second: _____ Third: _____

Fourth: _____ Fifth: _____ More than five: _____

Occupation

Academia: _____; Accounting/Finance: _____; Aerospace: _____;

Agriculture: _____; Army: _____; At risk student: _____;

Automotive: _____;

Banking: _____; Building/Constr. _____; Computer

_____; Consulting _____; Daycare _____; Education _____;

Emergency service _____; Engineering _____; Entertainment

_____; Fire industry _____; Government _____; Research and

development _____

_____; Health care _____; High tech _____; Hospt. admin. _____;

Hotel industry _____; Human resource _____; Insurance _____; Law

enforcement _____; Legal _____; Manufacturing _____; Medical

_____; Mental Health _____; Navy _____; Nursing _____;

Pharmaceutical _____; Psychology/Psychiatry _____; Publishing

_____; Real estate _____; Restaurant _____; Retail _____; Sports _____;

Other _____.

Religion: _____ (optional)

Race/Ethnicity (place a check or x to the response that applies to you)

Caucasian _____

African American _____

Indian American _____

Hispanic American _____

Spanish American _____

Asian American _____

Middle Eastern _____

Other _____

RESPONSE KEY: 0 = Not at all true

1 = A little true

2 = True

3 = Very true

You are now ready to answer the Personal Views Survey questions.

1. By working hard, you can always achieve your goal.

0 1 2 3

2. I don't like to make changes in my everyday schedule.

0 1 2 3

3. I really look forward to my work.

0 1 2 3

4. I am not equipped to handle the unexpected problems of life.

0 1 2 3

5. Most of what happens in life is just meant to be.

0 1 2 3

6. When I make plans, I'm certain I can make them work.

0 1 2 3

7. No matter how hard I try, my efforts usually accomplish little.

0 1 2 3

8. I like a lot of variety in my work.

0 1 2 3

9. Most of the time, people listen carefully to what I have to say.

0 1 2 3

10. Thinking of yourself as a free person just leads to frustration.

0 1 2 3

RESPONSE KEY: 0 = Not at all true

1 = A little true

2 = True

3 = Very true

11. Trying your best at what you do usually pays off in the end.

0 1 2 3

12. My mistakes are usually very difficult to correct.

0 1 2 3

13. It bothers me when my daily routine gets interrupted.

0 1 2 3

14. I often wake up eager to take up life wherever it left off.

0 1 2 3

15. Lots of times, I really don't know my own mind.

0 1 2 3

16. Changes in routine provoke me to learn.

0 1 2 3

17. Most days, life is really interesting and exciting for me.

0 1 2 3

18. Its hard to imagine anyone getting excited about working.

0 1 2 3

PVS III-R® Survey

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APPENDIX D

Center for Epidemiological Studies-Depression

CES-D

1. *During which visit is this interview taking place?*

- 1 () *Baseline*
2 () *8 Week*
3 () *6 month follow-up visit*
4 () *Other*

1.1 *Specify*

2. *Date of interview:* ____/____/____
month day year

3. *Interviewer's name:* _____
Last, First

This section deals with statements people might make about how they feel. For each of the statements, please indicate how often you felt that way during the past week.

0 = Rarely or none of the time (< 1 day)

1 = Some or a little of the time (1-2 days)

2 = Occasionally or a moderate amount of time (3-4 days)

3 = Most or almost all of the time (5-7 days)

-3 = Unknown

-4 = Refused

1. I was bothered by things that usually don't bother me.

0 () 1 () 2 () 3 () -3 () -4 ()

2. I did not feel like eating; appetite was poor.

0 () 1 () 2 () 3 () -3 () -4 ()

3. I felt that I could not shake off the blues, even with help from my family and friends.

0 () 1 () 2 () 3 () -3 () -4 ()

4. I felt that I was just as good as other people.

0 () 1 () 2 () 3 () -3 () -4 ()

5. I had trouble keeping my mind on what I was doing.

0 () 1 () 2 () 3 () -3 () -4 ()

6. I felt depressed.

0 () 1 () 2 () 3 () -3 () -4 ()

7. I felt that everything I did was an effort.

0 () 1 () 2 () 3 () -3 () -4 ()

8. I felt hopeful about the future.

0 () 1 () 2 () 3 () -3 () -4 ()

9. I thought my life had been a failure.

0 () 1 () 2 () 3 () -3 () -4 ()

10. I felt fearful.

0 () 1 () 2 () 3 () -3 () -4 ()

11. My sleep was restless.

0 () 1 () 2 () 3 () -3 () -4 ()

0 = Rarely or none of the time (< 1 day)
 1 = Some or a little of the time (1-2 days)
 2 = Occasionally or a moderate amount of time (3-4 days)
 3 = Most or almost all of the time (5-7 days)
 -3 = Unknown
 -4 = Refused

12. I was happy.

0 () 1 () 2 () 3 () -3 () -4 ()

13. I talked less than usual.

0 () 1 () 2 () 3 () -3 () -4 ()

14. I felt lonely.

0 () 1 () 2 () 3 () -3 () -4 ()

15. People were unfriendly.

0 () 1 () 2 () 3 () -3 () -4 ()

16. I enjoyed life.

0 () 1 () 2 () 3 () -3 () -4 ()

17. I had crying spells.

0 () 1 () 2 () 3 () -3 () -4 ()

18. I felt sad.

0 () 1 () 2 () 3 () -3 () -4 ()

19. I felt that people disliked me.

0 () 1 () 2 () 3 () -3 () -4 ()

20. I could not get going.

0 () 1 () 2 () 3 () -3 () -4 ()

CES-D Score ____

APPENDIX E

Profile of Mood States

NAME _____ DATE _____		Subject No. : _____
<p>Below are words that describe feelings and moods people have. Please read EVERY word carefully. Then fill in ONE space under the answer which best describes how you have been feeling <u>right now</u>.</p> <p>Suppose the word is <u>happy</u>. Mark the one answer which is closest to how you have been feeling <u>right now</u>.</p> <p>The numbers refer to these phrases:</p> <p>0 - Much unlike this 1 - Slightly unlike this 2 - Slightly like this 3 - Much like this</p>		
<p>1. Composed</p> <p>2. Angry</p> <p>3. Cheerful</p> <p>4. Weak</p> <p>5. Tense</p> <p>6. Confused</p> <p>7. Lively</p> <p>8. Sad</p> <p>9. Friendly</p> <p>10. Tired</p> <p>11. Strong</p> <p>12. Clearheaded</p> <p>13. Untroubled</p> <p>14. Grouchy</p> <p>15. Playful</p> <p>16. Timid</p> <p>17. Nervous</p> <p>18. Mixed-up</p> <p>19. Vigorous</p> <p>20. Dejected</p> <p>21. Kindly</p> <p>22. Fatigued</p> <p>23. Bold</p> <p>24. Efficient</p>	<p>25. Peaceful</p> <p>26. Furious</p> <p>27. Lighthearted</p> <p>28. Unsure</p> <p>29. Jittery</p> <p>30. Bewildered</p> <p>31. Energetic</p> <p>32. Lonely</p> <p>33. Sympathetic</p> <p>34. Exhausted</p> <p>35. Powerful</p> <p>36. Attentive</p> <p>37. Serene</p> <p>38. Bad tempered</p> <p>39. Joyful</p> <p>40. Self-doubting</p> <p>41. Shaky</p> <p>42. Perplexed</p> <p>43. Active</p> <p>44. Downhearted</p> <p>45. Agreeable</p> <p>46. Sluggish</p> <p>47. Forceful</p> <p>48. Able to concentrate</p>	<p>49. Calm</p> <p>50. Mad</p> <p>51. Jolly</p> <p>52. Uncertain</p> <p>53. Anxious</p> <p>54. Muddled</p> <p>55. Ready-to-go</p> <p>56. Discouraged</p> <p>57. Good-natured</p> <p>58. Weary</p> <p>59. Confident</p> <p>60. Businesslike</p> <p>61. Relaxed</p> <p>62. Annoyed</p> <p>63. Elated</p> <p>64. Inadequate</p> <p>65. Uneasy</p> <p>66. Dazed</p> <p>67. Full of pep</p> <p>68. Gloomy</p> <p>69. Affectionate</p> <p>70. Crowsy</p> <p>71. Self-assured</p> <p>72. Mentally alert</p>

BE SURE YOU HAVE ANSWERED EVERY ITEM

APPENDIX F

Quantikine HS

Human IL-6 Immunoassay

Catalog Number HS600B

For the quantitative determination of human Interleukin 6 (IL-6) concentrations in serum, plasma, and urine.

This package insert must be read in its entirety before using this product.

**FOR RESEARCH USE ONLY.
NOT FOR USE IN DIAGNOSTIC PROCEDURES.**

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INTRODUCTION

Interleukin 6 (IL-6) may be considered the prototypic pleiotrophic cytokine (1, 2). This is reflected in the variety of names originally assigned to IL-6 based on function, including interferon 2, IL-1-inducible 26 kDa protein, hepatocyte stimulating factor, cytotoxic T cell differentiation factor, B cell differentiation factor (BCDF) and B cell stimulatory factor 2 (BSF2)

(1). Once all the activities associated with the various names for IL-6 became connected with one common gene, the actual name IL-6 was proposed for this molecule (3). A number of cytokines make up the IL-6 cytokine family. Membership in this family is based on a helical cytokine structure and receptor subunit makeup (4, 5). For reviews on IL-6, see references 1, 2, 6 - 9.

Human IL-6 is a variably glycosylated, 22 - 27 kDa secreted glycoprotein. IL-6 is translated as a 212 amino acid (aa) molecule, with a 28 aa signal sequence and a 184 aa mature segment (10 - 13). It contains four cysteine residues and two potential N-linked glycosylation sites. An alternate splice variant of IL-6 was identified in monocytes and lymphocytes (14). This form is 17 kDa and 148 aa long and appears to lack a binding site for the IL-6 signal transducing molecule gp130. A virally encoded form of IL-6 in human herpes virus type 8 is 204 aa long and shows 25% aa identity to human IL-6 (15, 16). While it is active on human cells, it is not clear if its binding properties are comparable to those of IL-6 (16, 17). Mouse and rat IL-6 also have been cloned and are approximately 40% identical to human IL-6 at the aa level (18 - 20). Unlike human IL-6,

mouse and rat IL-6 lack potential N-linked glycosylation sites, but may be O-glycosylated (18).

Human IL-6 is active on both mouse and rat cells, while mouse IL-6 has no activity on human cells (19 - 21). Cells known to express IL-6 include CD8+ T cells, fibroblasts, synoviocytes, adipocytes, osteoblasts, megakaryocytes, endothelial cells (under the influence of endothelins), sympathetic neurons, cerebral cortex neurons, adrenal medulla chromaffin cells, retinal pigment cells, mast cells, keratinocytes, Langerhans cells, fetal and adult astrocytes, neutrophils, monocytes, eosinophils, colonic epithelial cells, B1 B cells and most likely, pancreatic islet beta cells (10, 14, 22 - 43). IL-6 production is generally correlated with cell activation. Circulating IL-6 can be found in the blood of normal individuals in the 1 pg/mL range, with slight elevations during the menstrual cycle, modest elevations in certain cancers, and large elevations after surgery (44 - 48). IL-6 has been described as both a pro- and anti-inflammatory molecule, a modulator of bone resorption, a promoter of hematopoiesis, and an inducer of plasma cell development (2, 7, 49). These activities are described in more detail in references 1, 2, 5, 7, and 50.

The Quantikine HS IL-6 Immunoassay is a 5.5 hour solid-phase ELISA designed to measure human IL-6 in serum, plasma and urine. It contains E. coli-expressed recombinant human IL-6 and has been shown to accurately quantitate the recombinant factor. Results obtained using natural human IL-6 showed linear curves that were parallel to the standard curves obtained using the Quantikine HS kit standards. These results indicate that the Quantikine HS IL-6 kit can be used to determine relative mass values for naturally occurring IL-6.

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Donohue, B., Covassin, T., Lancer, K., Dickens, Y., Miller, A., Hash, A., & Genet, J. (2004). Examination of Psychiatric Symptoms in Student Athletes. *Journal of General Psychology*, 163 (1), 29-35.

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