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“Anatomy of an Illness”: Control from a caregiver’s perspective:

2013 Cousins Lecture

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Abstract

Caregivers of loved ones with chronic illnesses experience an uncontrollable challenge with potentially negative behavioral and medical consequences. Extensive research has demonstrated immune and endocrine regulation can be significantly disrupted by negative behavioral factors based on both animal models and human studies. However, fewer studies have focused on how psychosocial interventions might reverse the negative consequences of stressors such as caregiving. The distress of caring for individuals with cancer has only recently begun to receive attention. These interventions addressing caregiver distress are rare overall and caregivers of patients receiving hematopoietic stem cell transplants (HSCT) have received even less attention. HSCT caregivers report feelings of loss of control. Animal studies suggest that control over aversive events can mitigate the negative consequences of stressors. Caregivers of allogeneic HSCT patients for blood cancers must be available 24/7 for three months or longer following stem cell infusion to closely monitor the recipients’ health and well-being. Does establishing a greater sense of control have positive impacts on caregivers? A randomized control trial of a cognitive behavioral stress management intervention for allogeneic HSCT caregivers is briefly described. A model of caregiver mental health which may potentially impact the patient’s quality of life is proposed. These relationships exist in a complex system that includes genetic influences, sex, social environment, and prior experience. This system fits well within recent formulations of a “complexity science” approach to health and well-being.

Keywords

Controllability; helplessness; hematopoietic stem cell transplant; caregiver; animal models; cortisol; inflammatory markers; natural cytotoxicity

“...my husband is getting ready to undergo a bone marrow transplant for his cutaneous T-cell lymphoma. We found out [husband’s name deleted] would need a transplant four months ago - one day after the birth of our first daughter... little focus is put on the caregiver in these situations, yet so much is demanded of us ... to take care of myself, my husband and our daughter... is a challenge...”

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This quote from an email received recently reflects the uncontrollable and adverse circumstances faced by a caregiver. It also sets the stage for the present overview and how the research program of my laboratory evolved from animal models addressing loss of control and complex social relationships in nonhuman primates (NHPs) to one in which we have begun to ask a significant question of psychoneuroimmunology (PNI): Can the untoward consequences of stressors and challenges on immune and endocrine regulation be reversed?

PNI has come a long way as a science from an off the map “dude” ranch [Tanque Verde Ranch, Tucson, Arizona, October 1-4 1986 (Cohen, 1987)] to early meetings in Colorado (Laudenslager, 1994) at which the PsychoNeuroImmunology Research Society (PNIRS) was ultimately chartered. At the early meeting in Arizona, we brought together behavioral and immunological scientists from almost a dozen US laboratories involved in PNI in the collegial setting of a dude ranch. There was no program beyond two tasks: 1) finding a common language for immunologists and behavioral scientists to converse and 2) addressing a fundamental question of the time, “*Does PNI have a future?*” Problems in communication remain as both areas have rapidly advanced scientifically. However 27 years later, I think we can easily answer the second question; PNI *had* a future then and furthermore PNI *has* an even greater future today.

The early years

At the time of the Tanque Verde Ranch meeting, the field of PNI was beginning an uphill battle with the medical community (Ader & Cohen, 1985). One paper in particular published in the influential *New England Journal of Medicine* challenged the field and threw the baby out with the bathwater after suggesting that psychosocial correlates of survival were non-significant contributors to outcome in cancer patients (Cassileth, Lusk, Miller, Brown, & Miller, 1985). Interestingly the same patients in that study had also received standard of care for their cancer including surgery, chemotherapy and/or radiation. Could these modalities be viewed as equally ineffective as well since all patients were in end stage disease? Should they also be dismissed? Of course not, all modalities (including behavioral aspects) are crucial for care of these patients. I entered the field of PNI around this time with a background in comparative physiology and animal behavior. Physiologists asked specific questions of regulated systems: 1) what is regulated, 2) what are the sensors, 3) what are the effectors, and 4) how accurate is the regulation? I recognized that a homeostatic system (this could easily translate to maintenance of health) combined behavioral and physiological responses in an integrated manner to achieve balance or homeostasis. The integration of behavior and physiology in the complex regulatory systems with which I became familiar during my early training in comparative physiology influenced my thoughts at the time I entered the nascent field of PNI. That behavioral and immunological systems were interrelated to promote the health of the organism seemed quite obvious in spite of arguments made at that time by many in the medical community. However the field of PNI has forced a paradigm shift in medicine as far as recognizing a place for behavioral factors in medical care and well-being. The next two decades provided case after case supporting behavior and immunity as interrelated with concrete means of intercommunication in meaningful but yet complex ways which filled many scientific journals including our society's journal, *Brain Behavior and Immunity*.

Animal Models

Animal models permitted important insights into behavior and immune relationships in the development of the science of PNI, partly because of control over factors largely impractical for human studies (Fleshner & Laudenslager, 2004; Laudenslager & Fleshner, 1994). An

adequate animal model includes a number of stipulations for supporting their relevancy: common etiology, phenomenology, pathophysiology, and efficacious interventions for the human condition they seek to model (Laudenslager, Boccia, & Reite, 1993). Nonhuman primates (NHPs) represented a socially complex species which afforded a number of advantages for investigating the relationship of social behaviors, not just stressor exposure, to immune regulation from both developmental and other perspectives (Coe & Laudenslager, 2007; Laudenslager & Kennedy, 2007). NHPs characterize a complex social organization that parallels humans and human society (Cirulli et al., 2009).

My first projects in PNI as a postdoctoral fellow in developmental neuroscience focused on biobehavioral development of young NHPs living in large social groups. Martin Reite had characterized the pathophysiology of brief maternal separation in socially housed macaque monkeys as an animal model of depression or grief. Brief removal of an infant's mother from their social group followed by reunion several days later was associated with altered circadian rhythms, cardiovascular regulation, and thermoregulation in the infant during the time the mother was absent [for review see (Reite, Short, Seiler, & Pauley, 1981)]. Reite suggested that I investigate the effects of this social separation model (*not isolation*) on immune function in infant monkeys. Reite had provocative data that effects of separating NHP peer pairs from each other on lymphocyte proliferation (e.g., reduced) (Reite, Harbeck, & Hoffman, 1981) were similar to those observed following a commuter train tragedy in which there were multiple cases of spousal bereavement (Bartrop, Lazarus, Luckhurst, & Kiloh, 1977). The peer study provided another indication of pathophysiological similarity between the impacts of loss in humans to social separation in young monkeys (Laudenslager & Reite, 1984).

We began a series of studies of the impact of brief maternal separations on immune regulation in the offspring spanning more than two decades [for reviews see (Coe & Laudenslager, 2007; Fleshner & Laudenslager, 2004)]. Similar to peer-pair separation as shown by Reite, separation of the mother of a bonnet macaque mother from her offspring was also associated with reduced lymphocyte proliferation to B and T cell mitogens in *both* the mother and her offspring both of which recovered after reuniting the pair (Laudenslager, Reite, & Harbeck, 1982). This was replicated in other species suggesting species similarity and the reliability of this response (Laudenslager, Held, Boccia, Reite, & Cohen, 1990). These observations not only replicated the impact of peer separation and the Bartrop study on lymphocyte proliferation, it further substantiated that a brief *psychosocial stressor* was sufficient to impact an *in vitro* measure of immune functioning and it recovered after the dyad was reunited.

Around that time Steve Maier and I met for the first time. Maier was familiar with the growing field of PNI but had not yet moved into that area (Maier, 2003). His model of loss of control and learned helplessness as well as a paradigm that was associated with an endogenous opioid analgesia when the rodents were re-exposed to uncontrollable foot shock, e.g., reinstatement (Maier, Drugan, & Grau, 1982) seemed particularly relevant. There were reports based on tissue culture studies at that time showing that beta endorphin enhanced immune measures such as lymphocyte proliferation (Gilman, Schwartz, Milner, Bloom, & Feldman, 1982). The helplessness model and opioid connection was intriguing from an immunological perspective. We considered potential outcomes of re-exposure to uncontrollable shock on lymphocyte proliferation. I predicted enhanced lymphocyte proliferation based on the tissue culture studies and Maier predicted suppression.

In this model, re-exposure to five very brief uncontrollable foot shocks the day following exposure to controllable or uncontrollable shock was associated with *suppressed* lymphocyte proliferation responses to B and T cell mitogens *only* in animals that received

shock uncontrollably on the preceding day. More importantly, the subjects *with prior control* over shock were no different than home cage controls or subjects restrained but not shocked on the preceding day (Laudenslager, Ryan, Drugan, Hyson, & Maier, 1983). Prior controllability was central to reversing the impacts of a now uncontrollable stressor. We pursued this model of immune modulation by controllability only to experience repeated problems with replication (Maier & Laudenslager, 1988). Some of these problems were reported at a meeting enumerating the many potential confounds (rodent strains, housing conditions, colony adaptation prior to testing, time of testing, source of the rodents, culture media, specific lot of fetal calf serum, and so on) investigated to identify the source of the variance none of which consistently resolved the problem (Maier & Laudenslager, 1988). Robert Ader elegantly commented after hearing of these problems:

“The immune response occurs in a neuroendocrine environment except that measured by immunologists.”

Those words stuck and significantly redirected efforts as far as immune markers applied by our group. What Ader was implying was that immunologists removed lymphocytes from the organism's natural environment in which they were naturally influenced by nervous and endocrine factors. They were placed in an artificial environment of supplemented media. Why would we expect consistency in this biomarker of a challenge which had previously affected the whole organism? Nick Cohen suggested that we consider an *in vivo* challenge using highly immunogenic keyhole limpet hemacyanin (KLH). Immunization with KLH reflects initial antigen processing by macrophages and consequent presentation to T cells resulting in the production of specific antibodies to KLH by the B cells (Maier & Laudenslager, 1988). This *in vivo* response, specific antibody levels, captured many aspects of an integrated immune response that took place in the organism not tissue culture. The rise in plasma IgM and IgG could be easily followed in order to address a number of important questions (Lockwood et al., 1996). With Moni Fleshner, a young graduate student working with Maier and I, we developed an enzyme immunoassay for detecting antibodies to KLH following immunization. We found that under a variety of different conditions, uncontrollable tail shock was consistently associated with reduced specific antibody levels to KLH compared to control conditions (Laudenslager et al., 1988). Fleshner went on to elegantly show that individual differences in the KLH response could be accounted for by *differences in the behavior* of individual rats responding to the behavioral challenge of territorial intrusion (Fleshner, Laudenslager, Simons, & Maier, 1989). Similarly in NHP models, influences of behavioral patterns and social interactions affected the way in which immune markers were disrupted (Boccia, Laudenslager, Broussard, & Hijazi, 1992; Boccia et al., 1997; Laudenslager et al., 1993). Purely psychological challenges were effective as physical challenges in modulation of immune readouts. Greater consistency in these immune indicators was also tied to using an *in vivo* challenge which was capitalized on by many other investigators as well (Ben-Eliyahu, Yirmiya, Liebeskind, Taylor, & Gale, 1991; Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998).

Noninvasive Assessment of the HPA

The question of a mechanism(s) for observed immune modulation by behavioral factors remained a challenge while the basic phenomenon of brain, behavior, and immune interactions were gaining credibility. Stressors clearly modulated immune regulation but how? Lymphocytes possessed a variety of receptors for recognizing not-self as well as regulatory molecules including cytokines and hormones. The hypothalamic pituitary adrenal (HPA) axis was a prime target for investigation due to the well-known impact of glucocorticoids on immune regulation at that time (Munck, Guyre, & Holbrook, 1984) and their established anti-inflammatory activity in clinical settings (Barnes & Adcock, 1993).

Collection of blood samples for assessing glucocorticoids while avoiding the stress created by the sampling process was a persistent problem.

A seminal review appeared around this time (Kirschbaum & Hellhammer, 1989) that turned the attention of many investigators to salivary cortisol as a practical approach for tracking the activity of the HPA [for a review in NHPs see (Laudenslager, Bettinger, & Sackett, 2005)]. In much the same manner in which a valid means of challenging the immune system *in vivo* became a focus, a noninvasive means of collecting biomarkers of the activity of the HPA would be equally advantageous. A focus on stress biomarkers in a particularly difficult population, preterm infants in a neonatal intensive care unit (NICU), first raised this question in our group. Blood samples were difficult to obtain from these high risk infants, what other options were available? Salivary cortisol seemed like an ideal option but how could it be collected?

Cortisol is a relatively stable steroid molecule. For example, some radioimmunoassay (RIA) protocols may heat samples to 90° C for 30 min to heat-inactivate binding proteins without affecting the bioavailability of the steroid for the RIA. Furthermore, corticosteroids can be melted without losing bioactivity (Hawes, Rock, Keogh, Lowry, & Calvano, 1992). Knowing cortisol's stability under adverse conditions, we began collecting saliva samples on specially cut Whatman filter papers which were dried and subsequently extracted based on a suggestion made at a meeting to Madalynn Neu who was collecting from the NICU infants. The absorbance characteristics of the filter papers were determined and found a relatively fixed area for these strips absorbed 100 µl of saliva. Following overnight extraction in assay buffer of a known area of the filter paper from the end of the filter, reliable measurement of cortisol in the extraction buffer could be achieved (Neu, Goldstein, Gao, & Laudenslager, 2007). These filter papers were incorporated into a compact booklet for recording collection time and holding the filters that could be stored at room temperature for up to a year without degradation of either cortisol or DHEA (Laudenslager, Calderone, Philips, Natvig, & Carlson, in press). Healthy adult subjects recorded time of collection on the booklet accurately compared to an electronic monitoring cap ($r^2 = .98$). Yet in spite of the careful recording of time of collection, considerable variance in the pattern of diurnal cortisol and DHEA remained. Individual variability in many factors such as emotional status of the subject at the time of collection can contribute considerably to salivary cortisol (Adam, 2006). Salivary cortisol reflects only a snapshot of the activity of the HPA at the time of collection. In reality, changes in HPA status over an extended period will have a more robust relationship to immunomodulation than acute or short term changes. Were there other approaches that provide cumulative measures of HPA activity?

A novel approach that provides considerable promise as a proxy to total HPA activity over a prolonged interval is measurement of cortisol found in hair segments (Davenport, Tiefenbacher, Lutz, Novak, & Meyer, 2006). In contrast to saliva samples that provide a snapshot of a highly variable system at the time of collection, hair cortisol may provide a proxy indication of retrospective HPA activity for the period of time represented by hair growth (Stalder & Kirschbaum, 2012). Hair grows approximately 1 cm/mo (Russell, Koren, Rieder, & Van Uum, 2012) and thus a 3 cm proximal length of hair is representative of the past three months of HPA activity. This is akin to hemoglobin A1c which reflects glucose control over the past three months (Saudek, Derr, & Kalyani, 2006). An advantage of hair cortisol is that it is available at the moment a subject is recruited into a study, a feature not available retrospectively for most biomarkers. Hair collection also avoids the problems of stress during collection, missed individual collections, poor adherence to collection times, or inaccurate recording of collection time which is present with saliva sampling (Broderick, Arnold, Kudielka, & Kirschbaum, 2004). Importantly hair collection is generally

noninvasive for the subject. Hair can be banked for an indefinite period of time allowing for assessment of cortisol in hair even collected from archeological samples (Webb et al., 2011).

What is the evidence that hair cortisol is a valid proxy marker of chronic HPA activity? For example, hair cortisol concentrations rise significantly in response to the stress of cross country relocation of a colony of NHPs (Fairbanks et al., 2011). Furthermore hair cortisol levels demonstrate significant heritability in a multigenerational, pedigreed colony of vervet monkeys (Fairbanks et al., 2011). In much the same way, salivary cortisol is also heritable (Kirschbaum, Wust, Faig, & Hellhammer, 1992) drawing parallels between the two markers. Similar to salivary cortisol (Loney, Butler, Lima, Counts, & Eckel, 2006), hair cortisol is associated with behavioral phenotypes, that is, high hair cortisol levels were correlated with reduced novelty seeking behavior in socially housed vervet monkeys housed in a large open field setting (Laudenslager, Jorgensen, Grzywa, & Fairbanks, 2011). In humans, maternal plasma cortisol levels rise during pregnancy (Mastorakos & Ilias, 2000) as do salivary cortisol levels (DiPietro, Costigan, Kivlighan, Chen, & Laudenslager, 2011). Hair cortisol follows a similar trend and it is correlated with the area under the diurnal salivary cortisol curve based on repeated contemporaneously collected saliva samples (D'Anna-Hernandez, Ross, Natvig, & Laudenslager, 2011). Much like plasma cortisol, hair cortisol varies with age in both NHPs (Laudenslager, Jorgensen, & Fairbanks, 2012) and humans (Dettenborn, Tietze, Kirschbaum, & Stalder, 2012).

There are downsides to hair cortisol that must be addressed. Other factors which impact cortisol assessed in hair such as hair processing remain unclear (shampoos, conditioners, straighteners, dyeing process, etc.). Recent unpublished work from our group suggests all of these factors may carry significant influences on cortisol measured in hair. Obviously male pattern baldness and shaved heads present a sampling problem for some subjects; body hair cannot substitute since it is thought to be less reliable (Stadler & Kirschbaum, 2012; Russell, et al, 2012). In spite of these problems, hair cortisol shows considerable promise for its use as a marker of cumulative HPA activity in a manner similar to salivary cortisol.

Controllability and Caregivers

Translation of the diverse observations from animal models and human populations to clinical implications is an important goal for future studies in PNI. Caregiving of medically ill patients is a long recognized stressor with numerous behavioral and physiological consequences (Gouin, Hantsoo, & Kiecolt-Glaser, 2008; Vitaliano, Zhang, & Scanlan, 2003). The majority of early caregiving studies focused on dementia caregivers and only more recently on caregivers of cancer patients (Kim & Schulz, 2008; Lutgendorf & Laudenslager, 2009; Rohleder et al., 2009). The majority of evidence clearly supports the negative consequences of caregiving include increased morbidity and mortality among caregivers and family members (Christakis & Allison, 2006). Caregiving represents a major public health concern.

The title of the present paper comes from a book by Norman Cousins, *Anatomy of an Illness* (Cousins, 1979), and for whom the Cousin's lectureship is named. In that book, Cousins describes how he gained control over a painful debilitating illness, ankylosing spondylitis (AS). Although the book is known popularly for his use of humor to reduce the pain, I offer that his approach provided a means for him to gain *perceived control* over pain associated with the illness. In fact a sense of helplessness (e.g., loss of control) as well as depression associated with ankylosing spondylitis is an important moderator of functional limitations and outcomes (Jang et al., 2011). Can interventions useful for patient populations be equally effective toward improving the dilemma(s) of their caregivers?

In the United States, there are roughly 42 million caregivers who provide 40 billion hours of care, representing an unpaid contribution to health care neighboring \$450 billion dollars/year (Feinberg, Reinhard, Houser, & Choula, 2011). According to the National Cancer Institute, family caregivers are integral to the survivorship team. Today the role of the caregiver in patient-centered care is becoming increasingly necessary (Gillick, 2013). However, family members and caregivers may show marked changes in various aspects of immune regulation including inflammatory markers (Kiecolt-Glaser et al., 2003), natural cytotoxicity (Vitaliano et al., 1998), responses to vaccines (Segerstrom et al., 2008), and wound healing (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). Yet few interventions have been tested in this highly distressed group (Harding & Higginson, 2003; Lutgendorf & Laudenslager, 2009; Simoneau et al., 2013).

Among caregivers, there are individuals caring for hematopoietic stem cell transplant (HSCT) patients (Bevans & Sternberg, 2012). HSCT patients must have a caregiver available 24/7 for the first 100 days post-transplant for transplant approval. A HSCT is a common treatment for a number of hematological malignancies and abnormalities including leukemia, lymphomas, aplastic anemia, and immunological deficiency states (Li & Sykes, 2012). Following chemical or intensive radiation ablation of their own lymphoid cells, hematopoietic stem cells, obtained from peripheral blood or bone marrow, are infused into the peripheral blood to regenerate the marrow. Transplanted stem cells may come from either the recipient (autologous) or closely matched donors (allogeneic). Allogeneic HSCTs have a greater risk for adverse effects and poor prognosis than autologous HSCTs, e.g., graft-versus-host disease (GvHD) [for review see (Blazar, Murphy, & Abedi, 2012)]. HSCT caregivers must prepare special neutropenic diets [although this practice is currently under reevaluation (Trifilio et al., 2012)], as well as monitoring for GvHD and infection, while maintaining an aseptic home environment after their loved one is discharged from the hospital. Caregivers of patients receiving allogeneic stem cell transplants (HSCT) report high levels of distress associated with caring for their loved one (Bevans & Sternberg, 2012; Simoneau et al., 2013). The perceived stress scale (Cohen, Kamarck, & Mermelstein, 1983) which assesses the individual's perceived control over life circumstances during the past month is elevated in HSCT caregivers above population norms (Simoneau et al., 2013). The opening quotation reflects the predicament of a HSCT caregiver.

Perceived loss of control and helplessness are prevalent feelings among patients with chronic illness (Diener, Kuehner, Brusniak, Struve, & Flor, 2009; Samwel, Evers, Crul, & Kraaimaat, 2006; van der Werf, Evers, Jongen, & Bleijenbergh, 2003) and caregivers of HSCT patients have similar perceptions (Simoneau et al., 2013) as do family members and caregivers in other critical care settings (Mitchell, Ferguson, Gill, Paul, & Symonds, 2013). Interventions tested by randomized control trials (RCT) that focus on alleviating caregiver feelings of loss of control and helplessness and stress are generally lacking (Harding & Higginson, 2003; Northouse, Kershaw, Mood, & Schafenacker, 2005; Thompson et al., 2007), particularly for HSCT caregivers (Langer, 2003). The US Surgeon General has provided a set of guidelines or a "prescription for caregivers" that includes: 1) attend to caregiver depression and anxiety, 2) identify resources and services in the community for the caregiver, 3) emphasize to the caregiver the need to take care of their own health, 4) teach caregivers about stress and its effects, 5) educate the caregiver with regard to the patient's illness, and 6) provide the caregiver with adequate tools for coping (Ulrich, 2007).

A randomized control trial (RCT) testing an intervention focused on allogeneic HSCT caregivers and their patients was recently completed (unpublished). This intervention, called PsychoEducation Paced Respiration and Relaxation (PEPRR) used a highly successful cognitive behavioral stress management model developed by Antoni for cancer patients (Antoni, 2013; Antoni et al., 2009) which we modified to meet the specific needs of the

allogeneic HSCT caregiver population. PEPRR was comprised of eight weekly 1-on-1 sessions in the clinic with a master's level therapist when the caregiver brought their patient for treatment follow up visits. The eight sessions included 1) an overview of the intervention and introduction to device-guided breathing for relaxation (Gavish, 2010), 2) stress and the mind-body connection, 3) how thoughts lead to stress, 4) approaches to coping with stress, 5) strategies for maintaining energy, 6) loss of control, predictability, and fear of the unknown, 7) managing changing relationships with the patient, and 8) locating the support they need in their community as well as within their family (unpublished). This study is presently unpublished but under review with regard to full methodological descriptions and primary and secondary outcomes at 3 months post-transplant.

Over a four year period, patient caregiver dyads were randomized from a consecutive sample of allogeneic HSCT patients presenting at a large regional transplant center serving the Rocky Mountain region. Caregivers were assessed with regard to behavioral, immune, and endocrine parameters at consenting prior to treatment randomization and subsequently at 1, 3, 6, and 12 months following transplant. The primary behavioral and physiological outcome variables were defined as 1) a measure of perceived stress or controllability (Cohen et al., 1983) and 2) the cortisol awakening response (CAR) (Laudenslager et al, in press). The CAR has been found to be variously affected in caregivers of Alzheimer's dementia, stroke, and depressed patients (Saban, Mathews, Bryant, O'Brien, & Janusek, 2012; Wahbeh, Kishiyama, Zajdel, & Oken, 2008).

Also collected from the caregivers were several secondary behavioral measures including depression, anxiety, HSCT-related PTSD-like trauma, mood, sleep, caregiver burden, mental and physical health [see Simoneau et al (in press) for a detailed description of measures]. Secondary physiological biomarkers included diurnal patterns of salivary cortisol and DHEA (Laudenslager et al., in press), natural cytotoxicity (Laudenslager et al., 1998), and plasma inflammatory markers CRP and IL-6 (von Kanel et al., 2006). The average age of the caregivers was about 54 years and represented mostly female (76%), spousal (70%) caregivers. Patients, whose average age was about 50 years, were *only* allogeneic HSCT patients predominately for leukemia (54%).

Prior to transplantation these allogeneic HSCT caregivers were quite distressed compared to population norms (Simoneau et al., 2013), similar to other's observations (Bevans & Sternberg, 2012; Bevans et al., 2011). However further unpublished analyses *at baseline* suggested that in spite of elevated distress, caregiver biomarkers were not significantly different from an age matched non-caregiving control group. In brief, PEPRR had significant effects for primary and secondary behavioral measures at three months and as well as secondary inflammatory biomarkers, plasma IL-6 and CRP (unpublished). All changes were in a direction toward improvement for the PEPRR group at three months. Parallel to other reports of differential protein transcription following intervention for breast cancer patients (Antoni et al., 2012), preliminary microarray analysis of protein expression pathways (measured at baseline and three months in a sub-study of the parent study) showed reductions in inflammatory, sympathetic, and oxidative pathways associated with assignment to PEPRR (unpublished).

A puzzling question was the relative lack of an effect of caregiving on biomarkers compared to a matched non-caregiving control group at baseline before the HSCT procedure (unpublished). This was in spite of the fact that the HSCT caregivers were reporting feelings of loss of control based on our primary outcome measure, the perceived stress scale, as well as elevated depression and anxiety (Simoneau et al., 2013). We began this project on a biomarker landscape suggesting caregiving and its many challenges were associated with changes in not only behavioral but also biomarkers of immune regulation including

inflammation, response to immunization, and wound healing (Gouin et al., 2008; Gouin & Kiecolt-Glaser, 2011; Kiecolt-Glaser, 1999).

Fifty-five papers from recent caregiver literature for the past 15 years (1998 - early 2013) were reviewed to determine the duration of caregiving challenge at the time of caregiver assessments in papers reporting biomarkers (cortisol, inflammatory markers, cytotoxicity) for any patient population (cancer, cognitive disabilities, child as well as adult patients, stroke and cardiac survivors). Of these 55 papers, only 15 (27%) reported duration of the caregiving challenge. The reported durations ranged from 22-287 months (mean = 79 mo.). From patient chart reviews of all dyads assigned to either TAU or PEPRR, the time since diagnosis of the illness requiring a transplant and the study baseline assessment was determined. A range of 2 – 146 months (mean = 26 mo.) was observed. The practical burden(s) of caregiving for allogeneic HSCT patients may not arise until the transplant process has begun. Although the caregiver stressor (major health change for the patient) was present on average about two years prior to baseline assessments, the full impact of the caregiving burden as indicated by biomarker modulation may be delayed for this particular group of caregivers. This is in contrast to caregiver biomarker studies in which assessments begin on average after six or more years of caregiving which likely becomes increasingly more burdensome. The rising burden, for example in caring for a patient with a progressive cognitive disability, differs significantly than that experienced by the HSCT caregivers in which the burden of caregiving responsibilities may actually decline with time as the patient improves following engraftment. Caregivers of allogeneic HSCT patients offer a unique perspective on features of caregiving: 1) a relatively short lived but intense burden and 2) a better prognosis associated with 70% survival/improvement (Li & Sykes, 2012) for HSCT patients compared, for example, to Alzheimer's patients where overall prognosis is poorer (Lyketsos et al., 2002).

To summarize, caregivers of allogeneic HSCTs are distressed at the time of transplant and the provision of an intervention offering stress and coping skills may influence feelings of control. The lack of any disturbance in the biomarkers prior to transplantation may be related to the shorter duration of exposure to challenges of caregiving. Caregivers are likely to benefit behaviorally from support interventions structured to meet their specific needs. The impact of interventions on processes such as inflammation is in need of further study. Caregiving is a complex stressor embedded within an interactive and constantly changing environment with regard to caregiver burden and biomarkers as illustrated in Figure 1.

These over-simplified relationships in Figure 1 reflect a model currently driving our approach to caregiver medical and behavioral well-being which ultimately impacts patient outcome and quality of life. All relationships exist on a background of multiple moderators that include genetic contributions such as single nucleotide polymorphisms (SNP) influencing, for example, the glucocorticoid receptors which affect stress responsivity (Derijk & de Kloet, 2008) or oxytocin receptor SNPs which impact HPA responsivity as well as the nature of the social relationship (Taylor et al., 2006). Characteristics such as sex and age contribute further to these relationships (Simoneau et al., 2013; Vitaliano et al., 2003) not to mention the role of social support (Kim & Carver, 2012). The impact of the dyadic relationship between the caregiver and the patient prior to entering the transplant process is poorly understood. Additionally the impact(s) of early and recent trauma in modulating the stress responsivity of both the caregiver as well as the patient (Langer, Brown, & Syrjala, 2009) need study. The contributions of these factors to the PNI of caregiving are ripe for research.

Resilient caregivers, portrayed as “human shock absorbers” (description from David Spiegel, 2013), take on this responsibility while facing many other challenges indicated in

the opening quotation. Some caregivers find benefits from this role (Brown et al., 2009; Kim, Schulz, & Carver, 2007). Conversely, there are likely to be caregiver subgroups with a greater need for interventions. Identifying these individuals should be a primary goal in the clinical setting but the specific characteristics of these individuals remain to be fully documented. Furthermore, does restoring a sense of control via an intervention enable the caregivers to *better support their patients* as well as mitigate personal longer term negative immunological and health consequences? Does an intervention for the caregiver indirectly improve the quality of life for their patient (broken arrows in Figure 1) and vice versa?

While experiencing a special day with her loved one day, a caregiver assigned to the PEPRR group following completion of the program wrote:

“... I breathed deeply and smiled. I was grateful for a moment’s peace and for a greater appreciation of the natural stress relievers that were everywhere...”
(*Chicken Soup for the Soul: Say Goodbye to Stress*, 2012, p.41-42.).

It is typically assumed a healthy and prepared caregiver is likely to provide better care compared to a poorly prepared or distressed caregiver but is this actually measurable as improved outcome for the HSCT recipient or a cancer patient? Currently we do not have answers available.

We began with a history of the negative impact of behavioral factors such as loss of control and social factors on a variety of biomarkers of immunity and neuroendocrine function in a number of animal models. Twenty seven years following our meeting in Arizona, PNI has shaped an exciting future for the next generation. However one must be cautious in identifying any single outcome measure as presumed to reflect stress. In spite of a central role of cortisol in overall stress homeostasis, stress does not necessarily equal cortisol. Challenge paradigms can have different effects on cortisol regulation depending on age (Gunnar, Talge, & Herrera, 2009) and acute versus chronic stress may create different relationships to HPA regulation (Miller, Chen, & Zhou, 2007). Neuroendocrine markers can be associated with considerable variability even under the best of conditions (Laudenslager et al., in press). Identifying the sources of this variance will be a major challenge for the next generation.

With the enormous intricacy of the system, new approaches to conceptualization of the health care system called “complexity science” (Hast, Digioia, Thompson, & Wolf, 2013; Jayasinghe, 2012; West, 2012) may be important to contemplate. Complexity science actually takes us back to a systems biology approach which was introduced in discussing the integration of behavior and physiology within any well-regulated systems. Stability in body temperature for example is an outcome of the combined activity of many systems: physiological, behavioral, and environmental. Similarly complexity science steps back and views the whole organism from a broader perspective including the social and medical systems in which the patient and their illness/health resides rather than focusing predominately on molecular pathways. Perhaps the pendulum is swinging away from molecular/genetic mechanisms to revisit an overall larger picture while appreciating molecular factors.

As we consider challenges for the next decade we need to consider the flip side of what got us to this point in the evolution of PNI, that is, stressors (negative events) were associated with disrupted immune regulation as core evidence linking brain, behavior, and immune regulation. Should we now focus on the opposite, that is, the salubrious effects of behavior? Can the negative consequences of stress or allostatic load (Korte, Koolhaas, Wingfield, & McEwen, 2005) be reversed by social interventions? Telomeres, protective structures on the ends of DNA which shorten with aging, may represent a fluid system that may be reversible

(Epel, 2012). Do positive health behaviors, wellness programs, or stress management impact these markers of aging such as telomere shortening (Epel et al., 2004)? For example, nutritional approaches appear promising; omega 3 supplementation is associated with lengthening of lymphocyte telomeres in at risk populations (Kiecolt-Glaser et al., 2013). Indications of down regulation of lymphocyte transcripts influencing inflammation and metastasis have been noted following patient intervention using the same program on which our caregiver intervention was based (Antoni et al., 2012). There is abundant reason to suggest that the next generation will move PNI in a direction undaunted by complexity with a focus on improving quality of life and health across all age groups within a complex interactive system. As we began, we will end, PNI has an exciting future!

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Highlight

This Cousins lecture highlights the progress of psychoneuroimmunology as seen through the eyes of the author who began working in this field in animal models over 25 years ago to translational approaches today.

Figure 1.

A conceptual model of the impact of a psychosocial intervention on caregiver behavioral and physiological markers and potential influences on their patient. The bidirectional interaction between stress, mood, and caregiver mental and physical health is proposed to be significantly influenced by a supportive cognitive behavioral stress management intervention that can be individualized to the needs of any caregiver group. Biomarkers move in a direction suggestive of improved caregiver health and well-being in the presence of such an intervention. However influences on the biomarkers are equally as complex as the behavioral factors. The caregiver is proposed to influence patient outcome and their quality of life (broken arrows) both directly (better care) and indirectly (patient sees their loved one as less distressed). Improved patient status will also have positive effects on the caregiver. This model is proposed to be completely interchangeable such that the patient could be placed in the location of the caregiver (that is receiving the intervention). However, both members of the dyad should be included in an intervention whenever medically possible. All of these relationships exist on a complex system including the effectiveness of the interventionist to background moderators such as genes, aging, the social environment, and early experience.