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Norman Cousins Lecture

"Anatomy of an Illness": Control from a caregiver's perspective

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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.

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"...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..."

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.

1. 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 and 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 et al., 1985). Interestingly the same patients in that study had also received standard of care for their cancer including surgery, chemotherapy and/or radiation. Could

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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*.

2. 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 and Laudenslager, 2004; Laudenslager and 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 et al., 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 and Laudenslager, 2007; Laudenslager and 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 material 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 et al. (1981a,b)]. 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 et al., 1981a,b) were similar to those observed following a commuter train tragedy in which there were multiple cases of spousal bereavement (Bartrop et al., 1977). The peer study provided another indication of pathophysiological similarly between the impacts of loss in humans to social separation in young monkeys (Laudenslager and 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 and Laudenslager, 2007; Fleshner and 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 et al., 1982). This was replicated in other species suggesting species similarity and the reliability of this response (Laudenslager et al., 1990). These observations not only replicated the impact of peer separation and the Bartop 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 et al., 1982) seemed particulary relevant. There were reports based on tissue culture studies at that time showing that beta endorphin enhanced immune measures such as lymphocyte proliferation (Gilman et al., 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 et al., 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 and 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 and 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 and 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

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