Plattsburgh State University of New York Scientia Discipulorum Volume 5 (2011)

Perspectives of Psychosomatic Medicine: An Integration of Psychoneuroimmunology and Epigenetics

Maria E. Kryza

Department of Psychology
State University of New York, College at Plattsburgh

ABSTRACT

After being subject to Descartes' fallacy for the past few centuries, it has now again been recognized that the mental state has an impact on health and disease, and it is becoming increasingly more evident that DNA alone does not predict health trajectories. Psychoneuroimmunology and epigenetics are two fields of science whose research supports those ideas. Psychoneuroimmunology aims to discover the mechanisms that connect our mind to the rest of our nervous, endocrine, and immune systems while epigenetics demonstrates that different environmental circumstances can produce different phenotypic outcomes that are unrelated to the actual DNA blueprint. An integration of the findings of those two fields may allow for a more accurate and complete understanding of individual health trajectories and may generate pathways to a more individualized treatment approach.

INTRODUCTION

Traditionally, orthodox medicine has viewed the patient as a passive victim of disease and a passive recipient of treatment. But this trend did not start until the 17th century with the dualistic worldview of René Descartes' who postulated that the mind and the body were two independent units. Psychology and medicine were, therefore, until recently, two separate fields for two separate entities – the mind and the body. However, long before Descartes, in about 400 BC, Hippocrates already said that it is more important to know the patient than his or her ailment (Ray, 2004). It is now again recognized that the mental state has an impact on health and disease. In addition to the notion of being victims of disease, a more recent development in science with its increasing focus on genes as the blue print of our bodies, has led to a sense of genetic determinism, or the idea that our genes have bestowed us with an inescapable heritage of good or ill health. Recent research in two groundbreaking fields of science, namely psychoneuroimmunology and epigenetics, provides evidence against those ideas. It appears that we are, in fact, in most cases *not* victims of our genes or disease, but rather that health, whether mental or physical, may often be manipulated from inside out.

Psychoneuroimmunology is a field of study that aims to discover the mechanisms that connect our mind to the rest of our nervous system, and our endocrine and immune systems. But what is "the mind"? Neuroscience is revealing that thoughts, feelings, beliefs, and hopes translate to chemical and electrical activity in the nerve cells of our brains; as thoughts are molded by experience, so is our brain (Ray, 2004). Therefore, when referring to "the mind" or psychological processes in this paper, such as thoughts, beliefs, and perceptions, they should be understood in terms of their biological correlates. The central nervous system (CNS) operates and communicates with the body on the basis of physiological processes, including electrical impulses, neurotransmitters, and hormones. The core of the CNS, the brain, is the source of cognition and executive control. Our thoughts, perceptions, and personality, therefore, may influence our physiology, including the immune system. Specific patterns of cognition and personality have been shown to relate to immune functioning; consequently, the question emerges of whether individuals could learn ways to directly affect their health status (Heyman, 1989).

The course of surgical recovery and how it is related to one's psychological state suggests this possibility. A variety of studies have demonstrated that stress delays wound healing, and that pain has

adverse effects on endocrine and immune function. It was shown that high preoperative fear and stress led to greater pain, longer hospital stays, and increased postsurgical complications (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998). In 1964, a pioneering study by Egbert, Battit, Welch, & Barlette examined the health effects a brief visit by an anesthesiologist on the day before surgery would have on the postsurgical recovery of the patient. During this visit, the patient was informed about typical postsurgical physical sensations and was taught a relaxation technique targeted to reduce pain. Compared to patients who did not receive this additional visit, patients who received consultative treatment were released from the hospital an average of 2.7 days earlier and required only half the morphine. Many similar studies have followed and confirmed the beneficial effects of a presurgical briefing (Kiecolt-Glaser et al. 1998). The cognitive difference of knowing what to expect after surgery has clear beneficial physiological consequences.

Research Epigenetics provides evidence against genetic determinism and demonstrates that different environmental circumstances can produce different phenotypic outcomes that are unrelated to the actual DNA blueprint. The various cells of the body share the exact same DNA even though a nerve cell is easily distinguished from a muscle cell. The "epi-genome" (epi = above, over; gr) is a mechanism that controls the expression of genes, and it allows for the differentiation of various cells as well as patterns of physiological responsiveness. Although such patterns of gene expression can be inherited, they are also primed during prenatal and early childhood development. Recent findings, however, are also suggesting that the epi-genome may be changed even in adulthood.

Twin studies offer an optimal methodological approach to understanding the reality of epigenetic mechanisms. The DNA of monozygotic twins is identical but that does not mean that that they share identical health trajectories. In fact, different health conditions have varying amounts of genetic influence as investigation of monozygotic twins shows. In psoriasis, for example, the genetic influence is very high whereas in multiple sclerosis (MS) it is weak (Chakravarti & Little, 2003). This means that if one monozygotic twin has psoriasis it is very likely that the other twin also has it. However, in the case of MS, if one of the twins has MS, the likelihood of the other one developing the disease as well, is only slightly higher than if the first twin did not have it. Similarly, it is possible for one monozygotic twin to develop autism while the other one progresses through childhood without disruption. Epigenetic mechanisms may explain the differences in the health trajectories between identical twins and provide evidence against genetic determinism.

Psychoneuroimmunology and epigenetics started out as two separate fields and developed initially in what appeared to be a parallel manner; however, the way their research expanded over the last few years it is becoming more and more apparent how their topics of interest and findings intertwine. They may even be two perspectives of the same observation. Changes in the body take place with the varying expression of genes, and the principles that underlie psychoneuroimmunology may be nothing more than a series of acute epigenetic changes. An integration of the findings of those two fields may allow for a more accurate and complete understanding of individual health trajectories and may generate pathways to a more individualized treatment approach.

PSYCHONEUROIMMUNOLOGY

Psychoneuroimmunology (PNI) postulates that there is a connection between the physiological processes that constitute the mind and physical health. The various environmental circumstances we encounter on a daily basis, whether social or physical, are interpreted not only by conscious thoughts, perceptions, and beliefs in the "higher" centers of the brain, but also affect "lower", unconscious areas. The physiological activity that constitutes this input, further affects somatic and visceral responses that

may also modulate immune system mechanisms. A study by Kiecolt-Glaser and Glaser (1984) investigated such physiological responses in conjunction with altering psychological states. They followed 40 first-year medical students for a period of one year and monitored the effectiveness of their immune system before and during exam periods. A depression of certain aspects of the immune system during those periods of stress was reported. The researchers found that the amount of time the students restricted their activity because of illness was associated with the exam periods and decreased cellular immunity. This suggests that the stress of the exams weakened the students' immune systems which was evident by an increased incidence of infectious disease during the periods before the exams.

Psychological states can also vary in terms of personality characteristics, which are more stable factors compared to the temporary and passing perception of stress prior to exams, as described above. O'Donnell, Brydon, Wright, & Steptoe (2008), assessed the protective nature of self-esteem, which has been connected to a decreased susceptibility to depression and abuse of tobacco, alcohol, and drug. This study examined the physiological effects self-esteem would have after exposure to stress. Participants were assessed for self-esteem using Rosenberg's self-esteem scale and exposed to two acute mental stressors, a speech task and a color-word task. Heart rate and a variety of plasma cytokines were examined for every participant pre and at a few points post-stress. O'Donnell et al. (2008) discovered that heart rate measures were lower among those with higher self-esteem and that this group also had smaller changes in plasma cytokines; both findings indicate a more adaptive self-regulation to stress. Overall, this study shows an association between global self-esteem and responses to stress and these differences may be a mediating factor between self-esteem and health.

Animal models also provide an effective way to study the basic mechanisms upon which PNI is founded. Azpiroz, De Miguel, Fano, & Vegas (2007), for example, found that different coping strategies in response to stress led to different susceptibility to the development of cancer metastases. In their experiment, mice were observed in social stress situations and categorized as either using passive reactive strategy, involving increased submission, fleeing, and avoidance behaviors, or active reactive strategy which was characterized by more attack and non-social exploration behaviors. In each of the groups, half of the mice involved in this experiment were inoculated with tumor cells. There were marked differences in the physiological reaction of the two groups to this inoculation: passive reactive mice exposed to tumor cells were shown to have a higher number of tumor foci and a higher level of corticosterone compared to the active reactive group. It appears as though the active reactive strategy is associated with a decreased susceptibility to the development of tumor foci. It remains to be answered whether learned coping strategy would result in modification of physiological cascades that lead to decreased susceptibility.

Molecular basis for the psycho-neuro-immuno connection

One way to illustrate the connection between the nervous and immune systems is in terms of cytokines. Cytokines are signaling chemicals released by various immune cells that act as a communication medium between cells (Kindt, Goldsby, & Osborn, 2007). Studies have shown that certain cytokines are responsible for a variety of so-called sickness behaviors which include decreased appetite, listlessness, fatigue and malaise, changes in sleeping patterns, and lack of interest in social activities. These behavioral patterns promote rest by discouraging activities that are metabolically expensive, such as foraging. In this way, they positively contribute to recovery; but their effect is not always beneficial. Certain cytokines are administered parenterally and used therapeutically in cancer patients. But this artificial increase of cytokines in those individuals gives rise to sickness behaviors; therefore, a side-effect of cytokine therapy is depression and anhedonia (i.e. the inability to experience pleasure) which has debilitating effects on quality of life (Kelley, Bluthé, Dantzer, Zhou, Shen, Johnson,

& Broussar, 2003). This suggests, however, that cytokines, produced endogenously or administered peripherally, exert an effect on the brain and on behavior.

Willette, Lubach, & Coe (2007) used the sickness behavior inducing effect of certain cytokines to illustrate the interaction between psychological state, environment, and physiological response. They administered Lipopolysaccharide (LPS) to rhesus monkeys to mimic bacterial infection and induce the release of proinflammatory cytokines which, as described, lead to sickness behavior and withdrawal. Those monkeys were then exposed to different environmental contexts. Activity, emotional and social behaviors, as well as a variety of physiological factors were determined. Depending on the context, LPS caused different behavioral and physiological reactions. In a human intruder paradigm context, a high stress situation, the effects of LPS appeared to be obviated, while in moderately stressful situation, administration of LPS led to similar changes in leukocyte and neutrophil release as would be expected in monkeys with a bacterial infection. The high stress situation appears to have overridden the cytokine-induced sickness behavior and expected physiological consequences. This means that mental states and perceived stress seems to have a significant effect on exogenous factors like infection ,which, in turn, supports the idea of a reciprocal relationship between the systems.

Cytokines have been found to be released by cells of other systems as well, such as the nervous system. In fact, the various signaling molecules in the body such as cytokines, neuropeptides, and hormones are not very clear cut categories and they have overlapping properties. A molecule acting systemically may be called a hormone but the same molecule acting locally could be referred to as a cytokine (Turnbull & Rivier, 1999). This gives further room for speculation of a reciprocity of interaction between the three systems. As early as the 1980s, researchers had begun to discover the interconnectedness of the neuroendocrine and immunologic systems by means of neuropeptides and their receptors. Chemicals released by the cells of the nervous system were shown to also have receptors in the cells of the endocrine and immune system and thus have been interpreted as a likely means of bidirectional communication. (Blalock, Harbour-McManamin, & Smith, 1985; Pert, Ruff, Weber, & Herkenham, 1985).

More recent discoveries have been made that in greater detail elucidate these mechanisms (Smith, 2007). For example, it was found that not only can NTs from the nervous system affect immune cells such as T-cells, but that T-cells themselves produce NTs (Levite, 2008). Bedoui et al. (2008) also studied the interconnectedness of the nervous and immune systems. Neuropeptide Y (NPY), a peptide released by nerves of the sympathetic nervous system, has been connected to a variety of immune functions; Bedoui et al. (2008) demonstrated that NPY receptors are present in human neutrophils, which are cells within the immune system. These receptors modulate important functions of neutrophils such as phagocytosis of bacteria. It was also shown that depending on the concentration of NPY, the neutrophil will either increase or inhibit phagocytosis of E. coli.

With regard to the immune system and how the nervous system affects it, it is interesting to observe in what way same immune cells can react differently to two different signals. Lipton, Bensch, and Karasek (1992) in their experiments with endothelial cells demonstrated how the idea of "mind over body" may work on a molecular level. When endothelial cells were exposed to histamine and epinephrine at the same time, the nervous system originating epinephrine overrode the local histamine signal.

The mind-body connection in terms of stress

The experience of stress is a good example of how cognition and perception can influence physiological mechanisms and health. The pathways through which physiological reactions to stress exert their effects on well-being have been studied extensively. Stress can be described by considering

contextual changes that require a response and are generally associated with a variety of visceral responses mediated by the nervous and endocrine systems. Generally stress can be defined as the psychological and physiological response to challenging or noxious circumstances. Those can be of physiological basis, such as weather, bodily trauma or disease, or of psychological basis, such as social context and interpretation of events (Daruna, 2004). In both cases, however, reactions among individuals vary because the way they perceive a situation affects the magnitude of subjectively experienced stress.

As an example of a stressful life circumstance, Gallagher, Phillips, Drayson, & Carroll (2009) investigated parents of children with developmental disabilities as compared to parents with normal children in their antibody response to vaccination. Depression, perceived stress, and child problem behaviors among other psychological factors were assessed before the start of the study, and antibody response was measured in participants one month and six months after administration of the vaccine. At both points parents who are caregivers had a poorer antibody response compared to control parents. This means that stressful life circumstances appear to be associated with the efficiency of the immune system. Behavioral characteristics of individual children are a mediating factor for differences in immunity of their parents. This study, therefore, provides evidence for a connection between environmental and psychological stressors and immunity.

The Hypothalamic-Adrenal-Pituitary (HPA) axis has been found to be one of the physiological mediators of stress. Perception of events, which takes place in the cerebral cortex, affects the hypothalamus. In a fight or flight situation, for example, the hypothalamus, via hormone corticotrophin releasing factor (CORT), activates the pituitary which in turn releases the hormone adrenocorticotropic hormone (ACTH), thereby causing the adrenals to release cortisol. Cortisol allows for a cascade of physiological changes that allow an individual to withstand a fight and flight situation. One of these is the suppression of the immune system. As the immune system requires a lot of energy, activation of the HPA axis, in response to a fight or flight situation, an evolutionarily more acutely life-threatening scenario, overrides immune activity which deals with exogenous but internal threats that are less acute. This can develop to be a problem when stress becomes chronic. Normally cortisol provides negative feedback to the pituitary and the hypothalamus, but with chronic stress this back regulation does not occur because the adrenal gland is continually given the signal from the hypothalamus and the pituitary gland to release more cortisol. This may be the reason why many diseases have been connected to stress. Elevated glucocorticoids, of which cortisol is a member, have been correlated to ill-health and diminished immune function. A variety of studies have connected the release of adrenal hormones to decreased blood leukocyte numbers, blood leucocytes being a good representation of the state of immune system activation (Dhabhar, 2002).

Johnson et al. (2002) conducted an experiment with rats which illustrates a connection between stress and the HPA axis. They wanted to find out whether a prior stressor exposure will affect the HPA response to further stressors. The primary stressor in this experiment was an inescapable tailshock (IS) and secondary stressors were either an infection with a bacterial endotoxin or the placement of the rats on a pedestal for a 24 hour period. All of these stressors served as HPA activation mechanisms. CORT and ACTH were significantly elevated after injection of endotoxin one hour after injection in rats that were exposed to prior IS, but not at later points compared to animals who did not receive IS. Being placed on a pedestal after IS also caused elevated CORT levels at first checkpoint after pedestal exposure (15 minutes after), but not at later points, compared to controls. This study shows that prior stressor exposure (IS) affects HPA reactivity to later stressors. However, these differences are short-lived. IS was only a one time acute prior stressor. Differences in HPA reactivity with chronic exposure to stress should

be examined but this study gives first clues that there may be a physiological difference in reactivity depending on whether a prior stressor was present.

Emotions as a mediating factor between the mind and the immune system

The realm of emotions is another way to look at stress and the mind-body connection. Emotions are closely related to the perception of an individual in a given situation and have been linked to a variety of immunological factors and, hence, to health and well-being. Just like the physiological response to stress, emotions are marked by characteristic physiological changes that are also mediated by the HPA axis. Emotional style may be a way to explain why people react differently to the same stressor and they may therefore provide a regulatory component to the negative effects of stress.

Studies have indicated that positive emotions may exert a protective effect on the immune system. Doyle, Gentile, & Cohen (2006), for example, have shown that the personality characteristic "emotional style", the propensity to experience predominantly positive or negative emotions, is linked to different responses to infection. In this experiment, participants were assessed for emotional style and exposed to a rhinovirus. An analysis of nasal cytokines following infection showed that Interleukin-6 (IL-6) was the best predictor of symptoms. IL-6 is an inflammatory cytokine released by Macrophages and endothelial cells that increases during immune activation and seems to be related to somatic and depressive symptoms following infection (Brydon, Walker, Wawrzyniak, Chart, & Steptoe, 2009). Participants in Doyle, Gentile, and Cohen's (2006) experiment that had a more negative emotional style exhibited more signs of illness both objectively and subjectively. When IL-6 was statistically controlled for in this group, a more positive emotional style was associated with lower IL-6 levels. This suggests that IL-6 may act as a biological mediator that links emotional style to differences in immune reactivity.

In another experiment, Brydon et al. (2009) examined how dispositional optimism, or the generalized expectation of good rather than bad things to happen in the future, relates to better health. This study also investigated the immune system and, specifically, how stress correlates with an increase in IL-6 and antibody response following a vaccine. Participants were randomly assigned to one of four different groups. Two groups received the vaccine and the others received a placebo. In each of these conditions, the participants either rested or engaged in two mental tasks which was considered a stress condition. It was found that high levels of optimism correlated with smaller IL-6 responses in both the stress condition and the rest condition following administration of the vaccine, suggesting that optimism offers a protective mechanism against inflammation induced by psychological stress and not specifically the vaccine. As IL-6 plays an important role in immunity and inflammation, this may be one of the mechanisms through which optimism exerts its protective effects on health. The participant group exposed to the vaccine followed by the stress condition also showed a strong correlation between optimism and antibody response, which means that optimistic people had a strong antibody response following vaccine and stress condition. Acute stress conditions have been shown in the past to enhance antibody response, but this response was especially pronounced in optimists.

Matsunaga, et al. (2008) were interested in what kind of physiological consequences there are in eliciting positive emotions. They developed a way to measure central nervous (via Positron Emission Topography or PET) and immune and endocrine (via blood sample) reactions at relatively the same time while male participants were watching a movie showing a favorite person (actress). Positive emotions were evoked in participant as measured by self-report via the visual analog scale. Natural killer (NK) cells and dopamine in periphery increased while positive emotions were experienced. A variety of brain regions were significantly more activated when watching the film clip with the favorite person, in comparison to the brain areas activated when a neutral film clip was watched. These results suggest that

central nervous, endocrine, and immune systems may be interrelated in eliciting immune function activation via the dopaminergic system. This study may suggest the significance of positive emotions and their protective role for the immune system; however, long-term effects still have to be examined.

While positive emotions appear to have a supportive role for the immune system, it was also shown that negative emotions correlate with a weakened immune system. Zorilla et al. (2001) showed that depression and stressors have an effect on immunity. One hundred and eighty studies are the basis of their meta-analysis and actual cellular changes were summarized for both depression and stressors showing a link between psychological states and immunological correlates. The following changes were observed: overall lycocytosis, mild reductions in absolute NK cell counts and relative T-cell proportions, small increases in CD4/CD8 ratios, and moderate decreases in T- and NK cell function. These immunological changes are associated with increased morbidity for diseases like cancer and infectious disease, increased hospitalizations and mortality among the elderly, and increased susceptibility to the common cold and upper respiratory infections.

Observations have been made that people with a negative outlook on life generally lead shorter lives and have poorer health. O'Donovan et al. (2009) examined the personality trait "pessimism," and they found it to be associated with a diminishing of the immune system. It appears that a person's trait pessimistic expectations correlate with immunosenescence (aging of the immune system). Telomere length was shorter in leukocytes of pessimistic people. Higher basal levels of IL-6 have also been found in pessimistic participants which is indicative of systemic inflammation and aging of the immune system. Both of these factors predict mortality. The mechanisms of how pessimism translates into increased IL-6 levels and shorter TL length still have to be examined.

Anger expression has been demonstrated to have negative effects on the progression of wound healing (Gouin, Kiecolt-Glaser, Malarkey, & Glaser, 2008). In this experiment, participants received a blister wound on the forearm. Anger control, as measured by anger scales, significantly predicted healing status of the wound at day four. Ability to control anger was associated with cortisol release as participants with lesser ability to control anger expression also secreted more cortisol. Cortisol is associated with healing by delaying it. Cortisol response to the mild stress of the administration of the blistering wound was great in participants with less efficient anger control which means that HPA reactivity is greater in those people. Anger control could be considered a self-regulatory mechanism. The question remains whether people with such physiological tendencies can learn to improve upon their ability to control anger and whether this would also translate into a change of their cortisol response.

EPIGENETICS

Ever since the discovery has been made that deoxyribonucleic acid, or DNA, is the source of what makes us unique as humans and individuals, a great amount of research has been dedicated to deciphering the genetic code and assigning meaning to it. A great emphasis has been placed on linking pathology to genes. This is due to a variety of single gene disorders that follow the Mendelian laws of inheritance. They require two copies of a recessive gene (one from the mother and one from the father) to be present in a genome to become phenotypically evident. Mendelian laws in conjunction with disorders such as sickle-cell anemia have led to the notion that disruptions of the DNA are the primary cause of human disease. While those correlations are true in some disorders, their emphasis has led to a belief in genetic determinism, meaning that our genes have endowed us with a certain health trajectory and destiny.

Most disorders, as twin studies have shown, originate from an interaction between genes and environment (G X E). A landmark study by Caspi et al. (2003) demonstrated the G X E interaction by examining the prevalence of depression among individuals with different alleles of the serotonin

transporter gene 5-HTT. There are two possible alleles of this gene; a short one (s) and a long one (l). As we inherit one copy each from our biological parents, there are three possible combinations one can inherit: s/s, l/l, and s/l. In a longitudinal format, Caspi et al. (2003) tracked the stressful life events of 847 children in two to three year increments from the age of three until 26. They found that individuals with the s/s genotype were increasingly more likely to experience a major depressive episode with increasing numbers of stressful life events. Probability for a l/l genotype increased only slightly with the number of stressful life events, while the s/l genotype had an intermediate probability between s/s and l/l. Caspi et al. (2003) also found the probability increased with amount of maltreatment the children experienced between the ages of three and eleven. The probability of a major depressive episode is equal at .30 for all three genotypes with no maltreatment. Even with severe maltreatment during this period of time this probability stays virtually the same for l/l genotypes, but increases to above .60 for s/s genotypes; s/l once again assumes an intermediate position at about .45.

The DNA included in each nucleus of our cells is merely a blueprint for the proteins, e.g. hormones, in our body which are the actual mediators and effectors of physiological activity. Not all genes are expressed at all times in all cells. Many genes are "silent" and have to first be "turned on" by signals from the environment in order to produce the proteins they code. A cell does not even need its DNA to live. Experiments that removed the nucleus from a cell have shown that a cell does not die with this process. It will deteriorate in time as it does not have the blueprint to replace proteins or synthesize new ones, but it can survive and be metabolically active for up to two months without its genes (Lipton, 2008). This means that physiological activity is not mediated by DNA but by the interaction of proteins.

An experiment by Lipton, Bensch, & Karasek (1991) illustrated the principle that cells are controlled by the environment rather than the genes by showing that the specialization of endothelial cells depends on the environment they are placed in. Endothelial cells were placed in different media in vitro, and it was observed that those cells changed their structure and function depending on the medium in which they were placed. When placed in an environment of inflammatory chemicals, those cells became similar to macrophages, for example. Interestingly, these changes took place even with a functional enucleation of the cells by destruction of their DNA with gamma rays (Lipton, 2008).

Research in epigenetics has shown that it is not our genes that control us, but rather their expression. Epigenetics, therefore, concerns itself with the mechanisms upon which gene expression depends, and explores how our genes may be controlled by environmental factors. Environment in this context refers to exogenous factors such as nutrition, climate, and stressful life events, but it may also refer to factors that originate from the individual such as attitudes, perceptions, personality characteristics, that are often primed during early childhood. These endogenous differences may originate from changes in hormone levels and different individual patterns of such changes.

Molecular basis of epigenetics

DNA methylation and histone modifications are the basic principles of epigenetics. DNA is a molecule that wraps around clusters of histone proteins. These units are called nucleosomes and a chain of nucleosomes forms chromatin. Gene expression is influenced by changes in the structure of chromatin; condensed chromatin is "silent" or "switched off," which means that the DNA included in this particular section of chromatin cannot be expressed, and open chromatin is active or "switched on" allowing for gene expression. Reversible patterns of DNA methylation and histone modifications are responsible for these changes in chromatin. Unmethylated DNA and high levels of acetylated histones make chromatin active. Specific developmental and/or biochemical clues are responsible for those reversible modifications of gene expression that make differentiation and communication between cells possible, but they may also

be the source of disease. Changes in hormone levels as well as dietary components and drug exposure may provide such clues. Pattern of DNA methylation may be modified by changes in diet and exposure to environmental chemicals. Methyl groups that are required for DNA methylation are aquired through diet, for example, and low dietary levels of folate, methionine or selenium may lead to neural tube defects, cancer, artherosclerosis. Methyl metabolism can be disrupted by environmental contaminants such as arsenic, fossile fuel emissions, contaminated drinking water, and cigarette smoke. Alcohol consumption and hormone replacement therapy have also been linked to changes in DNA methylation (Rodenhiser & Mann, 2006).

An applied example of these cellular observations are phenotypical changes that occur with the manipulation of the prenatal environment. Waterland and Jirtle (2003) showed that prenatal nutrition can influence genetic expression and thereby control the offspring's phenotype. The yellow agouti mice used in this experiment have an abnormal gene which normally causes them to have a yellow coat and to be obese. Pregnant yellow agouti females were given methyl supplementation with extra folic acid, vitamin B12, choline, and betaine. Even though the offspring shared the same agouti gene as the mother, their coat was not yellow and they ate much less than the offspring of yellow agouti mothers who did not receive the supplementation. This study illustrates the molecular changes of DNA methylation described above. The dietary methyl groups result in regions of the genome being transcriptionally silent. The experiment therefore illustrates that supplementation can modify gene activity.

Epigenetic effects have also been observed to extend over generations. Anway, Cupp, Uzumcu, & Skinner (2005) showed that environmental toxins can have transgenerational effects on phenotype. This means that there must be a transmission in the germ line through chromosomal or epigenetic changes. Gestating rats were exposed to environmental toxins, either an antiandrogenic or an estrogenic compound, during the gestational period where sex determination occurs. The offspring showed decreased sperm cell number and viability and an increased incidence of male infertility for four generations and altered DNA methylation in the germ line was found to be the cause. Although toxicity levels used for this study were higher than would be environmentally expected, the result suggests that environmental factors can affect phenotype negatively. Such environmental factors could potentially be controlled and prevented.

Stress: Connecting Psychoneuroimmunology and Epigenetics

As shown, stress is accompanied by a pattern of physiological responses, as studied in psychoneuroimmunology. The endocrinological changes that occur with stress also appear to have effects on gene expression. This is where a merger of the fields of psychoneuroimmunology and epigenetics takes place. PNI is based on the communication between cells within and across a variety of body systems which happen on the basis of cytokines and other communicating molecules. In the communication between two nervous system cells across a synapse, for example, neurotransmitters (NTs) in the synapse cause immediate changes in the charge of the postsynaptic membrane. But in addition to this, cascades of interactions can be set into place by the NTs at the postsynaptic membrane that can result in a long-term effect by turning on a gene in the postsynaptic cell. In this sense, "a presynaptic neurotransmitter communicate(s) with its postsynaptic receptors as to have a *presynaptic genome converse with a postsynaptic genome*" (Stahl, 2000). There appears to be a constant flow of information from nucleus to nucleus rather than just the surface communication seen at the synapse. The same may be true of communication between cells as mediated by cytokines. With the changes in cytokines that occur with stress, it appears that stress may therefore also lead to epigenetic changes.

Berry and Gasch (2008), for example, illustrated in their experiments with yeast in varying environments how stress brings forth changes in the epi-genome. Mild stress prepares yeast cells for

resistance to future high level environmental stress. This is called acquired stress resistance. The mild stress appears to set genetic expression cascades into motion that increase the cells' resistance to stress in the future. Such changes on a microbe level may indicate the magnitude of changes possible in more complex organisms.

In humans, these epigenetic effects have been observed while studying how prenatal and early childhood environment affect and prime offsprings' self-regulation skills to mitigate stress. There are individual differences in physiological reactivity to stress that appear to have genetic and epigenetic roots. The same stressor can bring forth a spectrum of responses and there seems to be individual patterns of such reactivity. Self-regulation of stress is mediated by the HPA axis and vagal tone and has important implications with regard to the health consequences of prolonged stress to an individual.

Wiebe et al. (2009), for example, examined the effects of postnatal tobacco exposure (PTE). PTE may manifest itself in different ways depending on the developmental stage of the child. Neonates and toddlers were examined in a cross-sectional study. The focus was exclusively on PTE and two known alleles of a gene coding for the D2 dopamine receptor (DRD2). Individuals with the A1+ genotype seem to have a higher risk of suffering from deficits in self-regulatory behavior caused by PTE. In this study, infants with the A1+ genotype and no PTE were more attentive to stimuli compared to the A1- genotype. These differences diminished when neonates with PTE were examined. In the toddler sample, children with PTE and the A1+ genotype performed more poorly on tasks involving executive function; however, children with PTE and A1- did not. This points to an inherited susceptibility to PTE for A1+ genotyped individuals. The experimental results hive some evidence for this gene-environment interaction; however, results are not clear because of some methodological problems, one of them being sampling differences in the two samples of this cross-sectional study. A longitudinal format would have been more revealing. Furthermore, it is more than likely that a variety of genes are involved in the susceptibility to PTE and self-regulation. Further studies are needed. This study, however, provides clues that neonatal environment has an impact on gene expression and lasting psychophysiological trajectories as effects of PTE were observed in toddlerhood. There is also an indication that environmental control allows adaptive phenotype control. Genotype may therefore in certain circumstances not be phenotypic destiny and environmental control may alleviate genotypic deficits.

Early childhood care and the priming of self-regulation skills

Maternal behavior in early development appears to have significant effects in the priming of self-regulation. Experiments with rats have been very revealing in this aspect. Francis, Diorio, Liu, & Meaney (1999) explored the question of whether differences in stress reactivity are due to genetic or environmental influences. Maternal behavior, specifically the level of licking/grooming and arched-back nursing (LG-ABN) by the mother, influences the offspring's individual differences in HPA reactivity and behavioral responses to stress. Offspring of mothers with high levels of LG-ABN have lower HPA reactivity and are less fearful in response to stress compared to offspring of mothers with low LG-ABN. The LG-ABN behavior is inherited by the offspring. Offspring of low LG-ABN mothers will also show low LG-ABN with their own offspring and the same is true for high LG-ABN offspring. To manipulate this, genetic offspring of low LG-ABN mothers was given to high LG-ABN mothers and vise versa, and observed in their levels of fearfulness. Genetic offspring of low LG-ABN mothers reared by high LG-ABN mothers showed the same levels of fearfulness as genetic offspring of high LG-ABN mothers reared by the same mother. When genetic offspring of high LG-ABN mothers was reared by low LG-ABN mothers, fearfulness behaviors of the offspring showed no difference compared to offspring born to and reared by low LG-ABN mothers. This points to a non-genetic transmission of these behaviors.

In a further experiment, Francis, Diorio, Liu, & Meaney (1999) set off to manipulate maternal behavior by handling the offspring of low LG-ABN mothers as this is known to increase LG-ABN behaviors. Mothers of handled low LG-ABN offspring did increase their LG-ABN to the extent that there was no difference in the amount of LG-ABN compared to high LG-ABN mothers. The offspring of the handled offspring showed the same characteristics as offspring of high LG-ABN mothers. Genetic expression, rather than genetic repertoire seems to be the source of the differences. Offspring of high LG-ABN mothers had increased levels of hippocampal glucocorticoid receptor mRNA expression, higher levels of central benzodiazepine receptors in the amygdala, and a lesser amount of corticotrophin-releasing factor mRNA in the hypothalamus. Handled low LG-ABN offspring showed no differences. Stress reactivity appears to be transmitted from generation to generation through behavior moderated by gene expression of genes in the brain.

Later experiments by Weaver et al. (2005) and Weaver, Meaney, and Szyf (2006) built on these results. Glucocorticoids receptors (GR) in the hippocampal region of rats provide a feedback mechanism to the stress response and are one way the intensity of the HPA response is mediated. Adult rat offspring of high LG-ABN mothers have higher hippocampal GR levels compared to low LG-ABN offspring. When this difference is eliminated, stress responses in adulthood are comparable in the two groups. Differences could be eliminated by centrally infusing adult low LG-ABN offspring with trichostatin A (TSA), a histone deacetylase inhibitor, or adult high LG-ABN offspring with methionine, an essential amino acid. These substances alter DNA methylation. TSA treated offspring, then, was comparable to high LG-ABN pups in anxiety behavior, HPA response, and hippocampal GR expression. The reverse was true for high LG-ABN rats infused with methionine. This study suggests that early-life experiences have a significant effect on gene expression and individual differences in reaction to stress. Furthermore, the reversal of the effect of maternal care through infusion of TSA or methionine, may indicate avenues for treatment past the critical periods in early childhood. Although the effects of TSA and methionine involved a large number of genes, the process appeared to be specific and a collapse of global gene programming was not observed. Further studies are needed to determine genome wide alterations of expression and the specific mechanisms involved in it as they happen with the infusion of substances such as TSA and methionine.

Human studies confirm the above findings that maternal behavior plays an important role in the priming of children's self-regulation skills. Propper et al. (2008) discuss the epigenetic mechanisms in the development of infant vagal tone. Vagal tone is considered another self-regulatory mechanism next to HPA reactivity and its purpose is inhibitory. The vagus nerve is responsible for slowing heart beat; it is therefore to some extent an antagonist to fight or flight responses. Dopamine receptor genes DRD2 and DRD4 and maternal sensitivity are considered co-varying factors in contributing to respiratory sinus arrhythmia (RSA) and RSA reactivity (vagal tone and reactivity respectively). In a longitudinal format, infants and their mothers were examined at ages of 3, 6, and 12 months. DRD2 is a risk allele for poor vagal tone; infants without this gene exhibited expected physiological regulation at 3 and 6 months, contrary to those with the risk allele who had poorer RSA withdrawal. At 12 months, infants with DRD2 whose mothers exhibited sensitivity, as assessed by observing the mothers' responsiveness, positive regard, and animation, had RSA withdrawal comparable to infants without the risk allele. Maternal sensitivity appears to play an alleviating role to the risk of a genetically-determined condition. This study suggests that genotype does not necessarily determine phenotype and that the environment may be manipulated to expresses the most adaptive responses. If risk gene DRD2 can be manipulated in this way, there are likely other risk genes that could be prevented from expression by adjusting the environment.

McGowen et al. (2009) provided evidence concerning a correlation between parental care and HPA activity. As shown above, maternal care has been shown to influence HPA activity in rats through an inhibition of the negative feedback mechanism that is caused by a decreased glucocorticoid receptor expression in the brain, in offspring of low LG-ABN mothers (Weaver et al., 2006). Here this trend was shown in humans. Postmortem examination of the hippocampi of suicide victims with a history of childhood abuse showed decreased levels of glucocorticoid receptor mRNA compared to suicide victims without a history of child abuse and controls. This study provides further evidence that early childhood is a critical period for the programming of the HPA stress response. Childhood abuse appears to lead to increased HPA activity and therefore decreased self-regulation ability. Epigenetic modifications possibly mediated by parental care may be responsible for these alterations.

JOINING PERSPECTIVES

Research in psychoneuroimmunology and epigenetics, although having started out on separate tracks, now begins to overlap. Each field examines the individual in different terms, but both attempt to explain the effects of stress and stress regulation. It becomes apparent that an integration of those two perspectives may be useful in the endeavor to explain individual differences in stress regulation and perception along with the associated health trajectories. A theoretical model is proposed that illustrates the connections between the two fields with regard to the individual (Appendix A).

Figure one shows the realms in which each field examines the individual. Psychoneuroimmunology researches the effects of the interactions between stress, perception, and state of mind, while epigenetics looks at the individual through the lens of environmental factors that have an effect on gene expression and the priming of self-regulation. In this way, each field discovers different nuances of an individual's physiology that may contribute to his or her health and wellbeing. There is an overlapping area of research interests that is concerned with the reactions of the individual organism to stress. Epigenetics looks at this in terms of priming of self-regulation while psychoneuroimmunology attends to the changes in immunological parameters as a consequence of stress according to various psychological factors.

Questions emerge as to how the findings translate into guidelines for adaptive living and to what extend maladaptive responses primed in childhood may be reversed or alleviated in adulthood. As cognition allows for malleability of psychological factors, as in the capacity to learn, the riddle that may potentially be answered by joining the perspectives of epigenetics and psychoneuroimmunology, is whether changes in cognition or learned techniques of relaxation, for example, may lead to epigenetic changes in the adult that counteract priming in childhood.

There are apparent beneficial effects in positive emotional style, dispositional optimism, and elicited positive emotions on the immune system, and possible negative outcomes with pessimism, anger expression, depression, and stress, as suggested by research in psychoneuroimmunology. Psychotherapy, by helping patients overcome non-adaptive thought patterns, may in this way also extend its effects not only on the individual's psychological health, but also their physical health by modulation of the immune system as a sort of "side-effect." Furthermore, stress reduction also appears crucial to increased health and wellbeing. The question remains, however, whether stress reduction and conscious changes in cognition and mindset will translate into improved physiological outcomes.

Several discoveries in clinical and applied research point to the possibility that the human capacity to think, learn, and direct attention may manipulate self-regulation of stress with physiological manifestations. Research examining the effects of meditation on health and wellbeing gives clues to the capacity of the individual to change their experience of stress and health trajectories and provides

evidence that the effects of early-childhood priming may be counteracted. Individual differences of subjective patterns of perception are rooted in habituated expectations that have resulted from life experience and may be related to epigenetic priming. Mindfulness meditation, a technique that requires the individual to be attentive of the present moment, may modulate perception and change patterns of expectation. It is also a method used to reduce the effects of stress in the body by guiding the person to a change in perception of acute circumstances. Rather than allowing the mind to wander, the individual practicing mindfulness refocuses their attention on any sensation or autonomic action thereby discouraging thinking. Paying attention to breath is a common technique, but one may also focus on the sensation of one's body in space and its contact to any surfaces, for example.

Witek-Janusek et al. (2008) examined immunological responses to mindfulness-based stress reduction (MBSR) in women recently diagnosed with early stage breast cancer compared to such women who did not undergo MBSR. The immune parameter levels for the MBSR groups improved significantly, while levels in the non-MBSR group worsened over three further assessments during and after the MBSR intervention. Quality of life and coping scale scores also improved in the MBSR group. This study provides sound evidence for the immunological effects of MBSR and supports the effectiveness of psychosomatic medicine.

Sharma et al. (2008) showed that the practice of meditation such as the relaxation exercise Sudarshan Kriya (SK) might help individuals regain physiological and psychological homeostasis after stressful events. It was found that SK practitioners had better antioxidant status as evidenced by enzyme activity and RNA levels. Prolonged life-span of lymphocytes mediated by an up-regulation of antiapoptopic genes and prosurvival genes suggested better immune status of SK practitioners.

Furthermore, Collins & Dunn (2005) documented a case study of a 54-year old female patient's recovery from Dermatomyositis, an immune disorder which manifested itself in the patient with a rash on the majority of her body with accompanied pain and proximally accentuated weakness. Transcendental meditation and visual imagery were practiced over a ten-month period during which pain, severity of rash, stressful events, and arm strength were recorded daily over 294 days. The results showed statistically significant improvements of the patient's condition for both mind-body techniques.

It appears as though mindfulness and meditation techniques are effective in some individuals, but it is yet to be discovered whether all can benefit from them and whether epigenetic priming can in fact be manipulated in this way. A common theme that emerges through the research presented here is the implication of individual uniqueness. One way to look at individual differences is in the light of self-regulation and personality; one may question if one's style of self-regulation predisposed one to be responsive to certain treatments but not to others. There appears to be a highly individualized susceptibility to the placebo effect, for example, which may be related to conditioning and epigenetic priming. Various psychological factors play a role in the effectiveness of a placebo and the unique and complex psychological background of every person implies the importance of individualized treatment (Pacheco-Lopez, Engler, Niemi, & Schedlowski, 2006). In the future, research may be able to classify individuals according to self-regulation and psychological tendencies, for example, and in turn suggest what kind of intervention will bring about the best responses any particular person, in a more precise manner than the trial and error method.

Current epigenetic research, however, does clearly support the importance of a nurturing environment in early childhood. A nurturing environment may not only protect the child and his or her family from ill health, but also equip the child with self-regulation patterns that will allow for the most adaptive stress responses and therefore better health later in life. A study by Blair et al. (2008) provides evidence for this as they demonstrated in their longitudinal study with 1,292 families, that high maternal

engagement during infancy correlates with a more adaptive stress response of the child, as mediated by the HPA axis, at both infancy and toddlerhood. This illustrates the importance of teaching new parents how to create a nurturing environment for their children and to be engaged in their development.

SUMMARY AND FINAL COMMENTARY

The research undertaken by the fields of psychoneuroimmunology and epigenetics underscores the fallacy of Descartes. Humans, or any organism for that matter, are units of motile interconnected systems that communicate unceasingly. The brain is part of this unit and our personality, our emotional states, our thoughts, beliefs, and perceptions are composed of conscious and unconscious processes in our brain that directly affect the rest of our bodies. The research presented also provides evidence against a deterministic mindset and strongly suggests that we have influence over our health trajectories. Additionally, it is continuously illustrates that stress has a major influence on our health and that perception and reactivity to stress is largely regulated by a combination of genetic and epigenetic mechanisms primed in early childhood.

There appears to be an incongruence, as on the one hand stress reactivity seems to be primed in childhood, but on the other hand some studies suggest that cognition may change epigenetic mechanisms. However, we have to bear in mind that experiments where priming of HPA reactivity was examined were mostly done with animals that do not have the cognitive ability to observe, control, and modulate reactivity on a voluntary basis. The reversibility of epigenetic priming in adult rats by administration of agents that change gene methylation suggests that similar changes may be attained in human adults. Pharmacological treatments that affect gene methylation and changes in nutrition are possible avenues, but additionally, the effectiveness of changes in cognitive strategies should be investigated. Studies have to be designed to examine whether individuals with non-adaptive stress reactivity who learn and utilize stress control techniques will have evidence of physiological, epigenetic changes. Much research still needs to be done in this field to understand the exact epigenetic mechanisms and how they may be influenced through learning and cognition.

The studies discussed in this paper do present with several limitations and the research in psychosomatic medicine is therefore still inconclusive. Much of the data is correlational and does not provide causative relationships. Additionally, all of the studies focus only on a very limited aspect of physiological effects. With current research methods it is not possible to take a more comprehensive approach, but this results in the possibility that a variety of effects are missed and not taken into account. Another limitation is that a great majority of the research is done with animals. This is necessary for ethical, temporal, and control reasons, but it cannot be concluded that effects are equal in humans. Humans are much more complex organisms and, as seen, the capacity to conscious thought appears to have a significant effect on physiology.

There is, nonetheless, substantial evidence speaking against genetic determinism that points to the importance of seeing the uniqueness of each individual. Individuality of each human is based on not only genes, but also the epigenome. While genes may increase the susceptibility to a variety of conditions given certain circumstances, those circumstances may be often be controlled. The specific conditions during early childhood, both social and environmental, can influence physiological reactivity to stress and therefore personality and lifestyle choices. These differences are visible in the susceptibility to the placebo effect, for example, and therefore to the effectiveness of various treatment and therapies. Rather than finding *the* cure, it may be more important to look at the individual and see what *went* wrong along their life path rather than looking at what *is* wrong acutely. Medicine, whether conventional or alternative, generally focuses on an acute observable problem that has to be fixed, but an individual is a dynamic

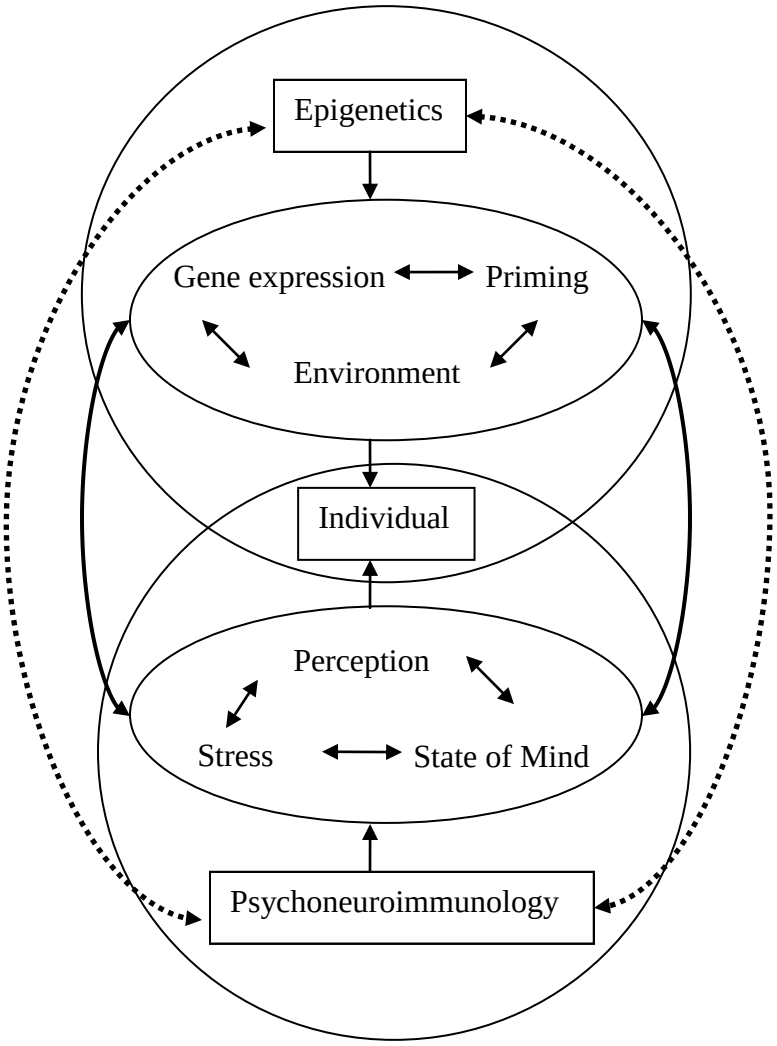
collection of biological and temperamental dispositions and experiences that are not dropped into varying environments but that create and select those circumstances. Wellbeing is a complex subject and therefore has to be approached from a much broader and deeper perspective (Friedman, 2008).

We have also seen that health, well-being, and susceptibility to disease generally comes from within the individual; therefore, the ability to create balance from within is crucial. Stress can disrupt this balance and various possibilities have been discussed of how the perception and experience of stress may be decreased, and wellbeing promoted. The mere knowledge of these mechanisms as described here can generate much impact within the individual by understanding that his or her health can be manipulated. A presurgical briefing correlated with improved recovery rates; a briefing on epigenetic mechanisms and how cognition may affect physiology could encourage an individual to strive for a more balanced life-style. Creating awareness among the general public on the scientific findings of the mind-body connection by healthcare professionals is crucial for improved medical outcomes and an increase in wellbeing.

Research in the future should focus on understanding epigenetic mechanisms as they function in different parts of the human body and the influence cognition can have on them. A multidisciplinary approach is necessary to gain greater understanding of the possibilities in treatment and prevention. Psychosomatic medicine is a subject that may have great impact on healthcare. Awareness of its findings and techniques may improve the quality of life for all. Much research is still needed to identify the exact physiological mechanisms of the G X E, mind-body interactions, but evidence points to a balanced and optimistic lifestyle as the most adaptive.

APPENDIX A

Figure 1



LITERATURE CITED

Anway, M.D., Cupp, A.S., Uzumcu, M., & Skinner, M.K. (2005). Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science, 308,* 1466-1469.

Azpiroz, A., De Miguel, Z., Fano, E., & Vegas, O. (2007). Relations between different coping strategies for social stress, tumor development and neuroendocrine and immune activity in male mice. *Brain, Behavior, and Immunity, 22,* 690-698.

Bedoui, S., Kromer, A., Gebhardt, T., Jocobs, R., Raber, K., Dimitrijevic, M., Heine, J., & Von Hörsten, S. (2008). Neuropeptide Y receptor-specifically modulates human neutrophil function. *Journal of Immunology, 195,* 98-95.

Berry D.B., & Gasch, A.P. (2008). Stress-activated genomic expression changes serve a preparative role for impeding stress in yeast. *Molecular Biology of the Cell, 19,* 4580-4587.

Blair, C., Granger D.A., Kivlighan, K.T., Greenberg, M.T., Hibel, L.C., Fortunado, C.K., Mills-Koonce, R., & Willoughby, M. (2008). Maternal and child contribution to cortisol response to emotional arousal in young children from low-income, rural communities. *Developmental Psychology, 44,* 1095-1109.

Blalock, J.E., Harbour-McMenamin, D., Smith, E.M. (1985). Peptide hormones shared by the neuroendocrine and immunologic systems. *The Journal of Immunology, 135,* 858-860.

Brydon, L., Walker, C., Wawrzyniak, A.J., Chart, H., & Steptoe, A. (2009). Dispositional optimism and stress-induced changes in immunity and negative mood. *Brain, Behavior, and Immunity, 23*(6), 810-816.

Caspi, A., Sugden, K., Moffitt, TE., Taylor A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., & Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301,* 386-389.

Chakravarti, A. & Little, P. (2003). Nature, nurture and human disease. *Nature, 421,* 412-414.

Collins, M.P., & Dunn, L.F. (2005). The effects of Meditation and visual imagery on an immune system disorder: Dermatomyositis. *The Journal of Alternative and Complementary Medicine, 11,* 275-284.

Daruna, J.H. (2004). *Introduction to Psychoneuroimmunology.* Burlington, MA: Elsevier.

Dhabhar, F.S. (2002). Stress-induced augmentation of immune function – The role of stress hormones, leukocyte trafficking, and cytokines. *Brain, Behavior, and Immunity, 16,* 785-798.

Doyle, W.J., Gentile, D.A., & Cohen, S. (2006). Emotional style, nasal cytokines, and illness expression after experimental rhinovirus exposure. *Brain, Behavior, and Immunity, 20,* 175-181.

Egbert, L.D., Battit, G.E., Welch, C.E., & Barlett, M.K. (1964). Reduction of postoperative pain by encouragement and instruction of patients. *Nee England Journal of Medicine, 270,* 825-827.

Francis, D., Diorio, J., Liu, D., & Meaney, M.J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science, 286,* 1155-1158.

Friedman, H.S. (2008). The multiple linkages of personality and disease. *Brain, Behavior, and Immunity, 22,* 668-675.

Gallagher, S., Phillips, A.C., Drayson, M.T., & Carroll, D. (2009). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior, and Immunity, 22,* 338-346.

Gouin, J.P., Kiecolt-Glaser, J.K., Malarkey, W.B., & Glaser, R. (2008). The influence of anger expression on wound healing. *Brain, Behavior, and Immunity, 22,* 699-708.

Heyman, S. R. (1989). Psychoneuroimmunology: Implication for clinical practice. In P. A. Keller & S. R. Heyman, *Innovations in clinical practice: A source book* (Vol. 8) (pp. 5-13). Sarasota, FL, England: Professional Resource Exchange.

Johnson, J.D., O'Connor, K.A., Deak, T., Spencer, R.L., Watkins, L.R., & Maier, S.F. (2002). Prior stressor exposure primes HPA axis. *Psychoneuroendocrinology, 27,* 353-365.

Kelley, K. W., Bluthé, R., Dantzer, R., Zhou, J., Shen, W., Johnson, R. W. & Broussard, S. R. (2003). Cytokine-induced sickness behavior. *Brain, Behavior, and Immunity. Special Issue: Biological mechanisms of psychosocial effects on disease: Implications for cancer control, 17*(1), 112-118.

Kiecold-Glaser, J.K., Page, G.G. Marucha, P.T., MacCallum, R.C., & Glaser, R. (1998). Psychological influences on surgical recovery: Perspectives from psychoneuroimmunology. *American Psychologist, 53,* 1209-1218.

Kiecolt-Glaser, J. K., Fisher, L. D., Ogrocki, P., Stout, J. C., Speicher, C. E., & Glaser, R. (1987). Marital quality, marital disruption, and immune function. *Psychosomatic Medicine, 49,* 13–34.

Kindt, T.J., Goldsby, R.A., & Osborne, B.A. (2007). *Kuby: Immunology*. (6th ed.). New York: W.H. Freeman.

Levite, M. (2008). Neurotransmitters activate T-cells and elicit crucial functions via neurotransmitter receptors. *Current Opinion in Pharmacology, 8,* 460-471.

Lipton, B.H. (2008). *The biology of belief.* Carlsbad, CA: Hay House.

Lipton, B.H., Bensch, K.G. & Karasek, M.A. (1991). Microvessel endothelial cell transdifferentiation: Phenotypic characterization. *Differentiation, 46,* 117-133.

Matsunaga, M., Isowa, T., Kimura, K., Miyakoshi, M., Kanayama, N., Murakami, H., Sato, S., Konagaya, T., Nogimori, T., Fukuyama, S., Shinoda, J., Yamada, J., & Ohira, H. (2008). Associations among central nervous, endocrine, and immune activities when positive emotions are elicited by looking at a favorite person. *Brain, Behavior, and Immunity, 22,* 408-417.

McGowen, P.O., Sasaki, A., D'Alessio, A.C., Dymov, S., Labonte, B., Szyf, M., Turecki, G., & Meaneym M.J. (2009). Epigenetic regulation of the glucocorticoids receptor in human brain associates with childhood abuse. *Nature Neuroscience, 12,* 342-348.

O'Donnell, K., Brydon, L., Wright, C.E., & Steptoe, A. (2008). Self-esteem levels and cardiovascular and inflammatory responses to acute stress. *Brain, Behavior, and Immunity, 22,* 1241-1247.

O'Donovan, A., Lin, J., Dhabhar, F.S., Wolkowitz, O., Tillie, J.M., Blackburn, E., & Epel, E. (2009). Pessimism correlates with leukocyte telomere shortness and elevated interleukin-6 in post-menopausal women. *Brain, Behavior, and Immunity, 23,* 446-449.

Pacheco-Lopez, G., Engler, H., Niemi, M., & Schedlowski, M. (2006). Expectations and associations that heal: Immunomodulatory placebo effects and its neurobiology. *Brain, Behavior, and Immunity, 20,* 430-446.

Pert, C.B., Ruff, M.R., Weber, R.J., Herkenham, M. (1985). Neuropeptides and their receptors: A psychosomatic network. *The Journal of Immunology, 135,* 820-825.

Propper, C., Moore, G.A., Mills-Koonce, W.R., Tucker Halpern, C., Hill-Soderlund, A.L., Calkins, S.D., Carbone, M.A., & Cox, M. (2008). Gene–environment contributions to the development of infant vagal reactivity: The interaction of dopamine and maternal sensitivity. *Child Development, 79,* 1377-1394.

Ray, O. (2004). How the mind hurts and heals the body. *American Psychologist, 59*(1), 29-40.

Rodenhiser, D., Mann, M. (2006). Epigenetics and human disease: Translating basic biology into clinical applications. *Canadian Medical Association Journal, 174,* 341-348.

Saurer, T.B., Ijames, S.G., Carrigan, K.A., & Lysle, D.T. (2007). Neuroimmune mechanisms of opioid-mediated conditioned immunomodulation. *Brain, Behavior, and Immunity, 22,* 89-97.

Sharma, H., Datta, P., Singh, A., Sen, S., Bhardwaj, N.K., Kochupillai, V., Singh, N. (2008). Gene expression profiling in practitioners of Sudarshan Kriya. *Journal of Psychosomatic Research, 64,* 213-218.

Smith, E.M. (2007). Neuropeptides as signal molecules in common with leukocytes and the hypothalamic-pituitary-adrenal axis. *Brain, Behavior, and Immunity, 22,* 3-14.

Stahl, S.M. (2000). *Essential Psychopharmacology* (2nd ed.). New York: Cambridge University.

Turnbull, A.V., & Rivier, C.L. (1999). Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: Actions and mechanisms of action. *Physiological Reviews, 79*(1), 1-71.

Waterland, R.A., & Jirtle, R.L. (2003). Transposable elements: Targets for early nutritional effects on epigenetic gene regulation. *Molecular and Cellular Biology, 23,* 5293-5300.

Weaver, I.C.G., Champagne, F.A., Brown, S.E., Dymov, S., Sharma, S., Meaney, M.J., Szyf, M. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. *The Journal of Neuroscience, 25,* 11045-11054.

Weaver I.C.G., Meaney, M.J., & Szyf, M. (2006). Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *PNAS, 103,* 3480-3485.

Wiebe, S.A., Andrews Espy, K., Stopp, C., Respass, J., Stewart, P., Jameson, T.R., Gilbert, D.G., & Huggenvik, J.I. (2009). Gene-environment interactions across development: Exploring DRD2 genotype and prenatal smoking effects on self-regulation. *Developmental Psychology, 45,* 31-44.

Willette, A.A., Lubach, G.R., & Coe, C.L. (2007). Environmental context differentially affects behavioral, leukocyte, cortisol, and interleukin-6 responses to low doses of endotoxin in the rhesus monkey. *Brain, Behavior, and Immunity, 21,* 807-815.

Witek-Janusek, L., Albuquerque, K., Chroniak Rambo K., Chroniak, C., Durazo-Arvizu, R., & Mathews, H.L. (2008). Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. *Brain, Behavior, and Immunity, 22,* 969-981.

Zorilla, E.P., Lubowsky, L., McKay, J.R., Rosenthal, R., Houldin, A., Tax, A., McCorkie, R., Seligman, D.A., & Schmidt, K. (2001). The relationship of depression and stressors to immunological assays: A meta-analytic review. *Brain, Behavior, and Immunity, 15,*199-226.