PREFACE

While the origins of the concept that emotional status and mental processes are linked to physical health or disease can be tracked back to antiquity, the scientific basis of our understanding of the underlying mechanisms was largely set up in the late part of the 20th century.

The understanding of the neurochemical, immunological, endocrinological, neurobiological and psychological implications of the cross-talk between the systems offers exciting approaches to the management of various pathological conditions, in which the regulation between these systems is disturbed. Nevertheless, psychoneuroimmunology has tended to be marginalized as a subject of limited scientific merit up to now.

The 1st Alfried Krupp Wissenschaftskolleg Symposium focused on mind-body-interrelationships which influence the host's ability to combat bacterial infections. Our current hypothesis regarding the activity of the immune system in systemic infection includes both uncontrolled hyperinflammatory responses as well as unresponsiveness due to an anti-inflammatory cytokine bias. The type of response is determined by many factors, including the patients coexisting conditions. Among them the body-mind-interactions are not yet understood. Researchers and clinicians as well as psychologists from different scientific backgrounds discussed at the 1st Alfried Krupp Wissenschaftskolleg Symposium their results.

The data presented at the meeting underlined the importance of an integrated strategy, because – as this booklet demonstrates – it is not possible to obtain full understanding of immunoregulatory processes without considering the organism and the external and internal environment in which immune responses take place.

We are looking forward to meet you in 2006 at the 2nd Alfried Krupp Wissenschaftskolleg Symposium on Stress, Behaviour and Immune Response.

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STRESS, GENES, CHRONIC INFLAMMATION, AND THE DISEASES OF AGING: A PNI OVERVIEW

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In the past 15 years there has been an explosion of articles that demonstrate how psychosocial inputs to the central nervous system alter our physiology leading to symptom formation and increased susceptibility to a variety of disease processes. The field of psychoneuroimmunology (PNI) has been a major contributor to defining the pathways by which common stressors initiate neuroendocrine and immunologic dysregulation. In this overview I will give a snapshot of a large body of literature that indicates that psychosocial stress leads to human pre-disease manifestations, influences genomic structure and function, and sets into play a variety of mechanisms involved in the diseases of aging.

THE MIND AND PRE-DISEASE MANIFESTATIONS:

Stress activates a cascade of physiologic responses with the activation of the sympatho-medulary-adrenal (SAM) axis, the hypothalamic-pituitary-adrenal (HPA) axis and associated immune responses being the best characterized. Whatever the stressor, responses differ greatly between individuals. The meaning of the stress to an individual, his/her resiliency, and genomic differences such as genetic polymorphisms dictate his/her physiologic response. For example, in a longitudinal study of a representative birth cohort it was found that a functional polymorphism in the promoter region of the serotonin transporter gene moderated the influence of stressful life events on depressive symptoms, diagnosable depression and suicidality (1).

Severe, repeated and/or chronic stress can lead to persistent elevation of the physiologic response or a slower return to baseline. Conversely a failure to mobilize an appropriate physiologic response to stress may occur. A diminished cortisol response is often observed in individuals with post-traumatic stress or the chronic fatigue syndrome (2,3).

Stress-induced endocrine-immune dysregulation may produce common symptoms often not associated with any disease diagnosis (Figure 1). For example, the common symptoms of fatigue, memory loss, and pain my reflect hormone and/or immune dysregulation in the central nervous system and/or musculoskeletal system. Excessive cortisol and cytokine secretion negatively effect cognitive functioning (4,5) and the musculoskeletal system (6,7). The catabolic influence of pro-inflammatory cytokines on the musculoskeletal system may be mediated by producing abnormal metabolism of myosin, an important muscle contractile protein (7).

Chronic stress associated with the absence of resistance resources may be important in the genesis of symptoms like pain. A study of 126 patients with fibromyalgia pain was compared to individuals with chronic pain from osteoarthritis. They were interviewed weekly for 12 weeks for perceived interpersonal stress and positive interpersonal events. They did not differ in negative affect, depression, or anxiety but fibromyalgia patients were characterized by lower levels of positive affect particularly during stressful weeks (8).
Repeated physiologic maladaption produced by stressful life events, environmental influences, and associated poor health behaviors produces symptoms (Sx's) in the gap between disease onset and diagnosis (Figure 2). Over time, the march of continual

psychosocial stress induces chronic physiologic dysregulation in common measures as blood pressure, weight, and blood sugar. Eventually this maladaption leads to diseases such as diagnosable coronary artery disease and congestive heart failure (Figure 3).

Once the disease is established, the same stressful processes that contributed to its pathogenesis now can affect disease outcomes such as mortality rates. For example, an unhappy marriage in individuals with congestive heart failure can markedly shorten an already compromised lifespan (9).

MIND AND THE GENOME

There has been much interest in how the genome can modify personality and mood. A Medline search in October of 2004 for articles dealing with genetics, personality and mood produced 2910 citations. In contrast, there is much less information on stress and behavioral modification of the genome. This information, however, is beginning to become available.

It is well documented that genetic defects occur in the pathogenesis of most cancers. The role that genetic and environmental factors play in its pathogenesis was the subject of a report from Sweden. Lichtenstein and colleagues studied 44,000 pairs of twins listed in the Swedish, Danish, and Finnish twin registries in order to estimate the risk of cancer at 28 anatomical sites for twins of individuals with cancer (10). They found that inherited genetic factors made a relatively minor contribution to susceptibility to most types of sporadic cancer. They argued that non-shared “environmental factors” were responsible for these findings.

What role did stress play in the twin that developed the neoplasm? Could stress and subsequent maladaptive mechanisms have been a mediator of carcinogenesis in the twin who developed cancer?

Chronic stress can alter gene expression. It has been shown that chronic stress in caregivers of spouses with Alzheimer’s dementia down regulates gene expression of lymphocyte GH mRNA production which has been shown to play a role in gamma-interferon production (11,12).

Moreover, stress could more significantly transform gene structure for extended periods of time. Meaney’s laboratory has shown that rodent offspring of mothers with decreased pup licking and grooming have altered the epigenome at a glucocorticoid receptor gene promoter in the hippocampus (13). This glucocorticoid receptor deficiency was associated with enhanced corticosterone secretion following restraint stress. These differences emerged during the first week of life, were reversed by cross fostering, persisted into adulthood, and were associated with altered histone acetylation and transcription factor binding to the glucocorticoid promoter.

Also, chronic stress in mothers of children with cancer produced increased oxidative stress and a decrease in cellular telomere length in peripheral blood mononuclear cells of these mothers. Telomere length is a reflection of accelerated cellular senescence and women

with the highest perceived stress in this study had shorter telomeres on average by the equivalent of 9-17 years compared to the low stress women (14).

These latter studies strongly support the notion that genetic expression can be altered transiently or for long periods of time by epigenetic alterations produced by psychosocial input.

MIND AND CHRONIC INFLAMMATION

Stress and subsequent endocrine-immune interactions may be important events in the pathway to disease. Chronic elevation of cortisol from stressful life events and/or relationships, even though remaining within population normal ranges, is associated with multiple disease outcomes (Figure 4) (15).

The relative risk for all-cause mortality in chronically stressed caregivers is 63% higher than in non-caregiving controls (16). This finding may be related to the observation that caregiving for a spouse with Alzheimer's dementia can produce an increase in blood pressure, depressive-like symptoms, infectious illness, delayed wound healing, and a decreased response to influenza and pneumococcal pneumonia vaccines (17-22). These health effects may be quite long-lasting as an altered immune response to influenza vaccination in caregivers may persist long after the spouse has died (23).

Excessive IL-6 secretion may be responsible for some of these findings. There is a large body of evidence that IL-6 may be an important cytokine linking a variety of health behaviors with disease. Interleukin-6 is produced by immune and immune accessory cells and is also secreted by non-immune cells and organs like the myocardium (24). IL-6 functions both as a hormone and proinflammatory cytokine. In its role as an endocrine, its secretion is stimulated by catecholamines which then stimulate CRH-release leading to subsequent increase in ACTH and cortisol secretion (24). It also stimulates arginine vasopressin release from the hypothalamus and is inhibited by cortisol, androgens and estrogen (Figure 5). The increase in plasma IL-6 levels with age partially reflects the elevated catecholamine secretion and diminished sex steroids levels in aging individuals.

Increased IL-6 levels are associated with aging, obesity, sedentary lifestyle, smoking, anger/hostility, low socioeconomic status and depression (23, 25-28).

Depressive-like symptoms and depression have been associated with multiple health risks. Even a modest number of depressive symptoms can increase basal serum levels of IL-6 (29). The addition of a pro-inflammatory stimulus like an influenza vaccination produces persistent elevation of IL-6 several weeks after the inoculation whereas this prolonged inflammatory response does not occur in non-caregivers (29).

Numerous diseases including coronary artery disease, Type 2 diabetes mellitus, osteoporosis, rheumatoid arthritis, cancer, autoimmune disorders, and congestive heart failure have been associated with elevated IL-6 concentrations. A 6-year longitudinal study in Alzheimer caregivers and controls examined the relationship between chronic stress and IL-6 production (23). Aging produced an increase in IL-6 levels but the slope of increase in the caregivers was four times that found in the non-caregiving controls. Moreover, the mean rate of increase in IL-6 levels among former caregivers was no different then among current caregivers even several years after the death of the ill spouse. There were no

systematic group differences in chronic disease, medications, or health-related behaviors that might explain the caregiver's steeper IL-6 slope. These observations suggest a mechanism whereby chronic stress may enhance susceptibility to a variety of chronic diseases by prematurely aging the immune response.

MIND AND THE DISEASES OF AGING

The health implications of persistent inflammation accentuated by stress are far-reaching. Dementia, cancer, and cardiovascular disease all have inflammatory processes as part of their pathogenic landscape. Investigators have found that increased IL-6 production from microglia in irradiated brain hippocampus cultures decreased new neuron development and this process was restored toward normal with an anti-inflammatory agent (30). The hippocampus is responsible for memory and learning, therefore, persistent inflammation may be involved in the pathogenesis of human dementia.

In the cardiovascular literature, the number of articles dealing with the relationship of chronic inflammation and cardiovascular disease has accelerated during the past decade. Again, IL-6 shows up as a risk factor along with C-reactive protein (CRP), which is an inflammatory peptide made by the liver, the secretion of which is stimulated by IL-6.

Elevation of CRP and IL-6 predict cardiovascular disease (31). They act in concert with other inflammatory molecules to initiate and enhance arterial plaque formation (32). The health behaviors and psychosocial factors (depression, low socioeconomic status, obesity, smoking, and sedentary lifestyle) including chronic stress, associated with increased Il-6 levels are all established risk factors for cardiovascular disease (31) and diabetes mellitus (33).

Several cancers have now been shown to be associated with elevated IL-6 and TNF-alpha levels which predict metastases and mortality from prostate and renal cell cancer (34,35). Chronic stress, elevated pro-inflammatory cytokine levels, and subsequent inflammation appear to be involved in the promotion and/or progression of cancer (36).

Evidence suggests that chronic inflammation may play a central role in carcinogenesis by inhibiting apoptosis and stimulating growth factor production. The mediator of this effect appears to be enhanced activity of the cellular transcription factor, NF- kappa B (36). Moreover, TNF-alpha and IL-1, stimulation of the production of NF-kappa B is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression (37).

Poor social relationships have been reported to increase cancer mortality risk (38). It has been suggested the psychosocial stressors which initiate endocrine-immune dysregulation could influence tumor progression (39,40). Abnormal endocrine concentrations and/or rhythms have been reported in breast cancer (41,42) and a loss of cortisol diurnal variation has been associated with early mortality from breast cancer (40). In mice, destruction of the suprachiasmatic nucleus which eliminates diurnal variation of many biologic systems including cortisol causes animals to die earlier from implanted carcinoma and sarcoma than sham-operated controls (43). Therefore, psychosocial stress may produce endocrine/immune disturbances that promote chronic inflammation (36) and subsequent cancer promotion and/or progression.

Chronic stress may play a role in the development of inflammation and induction of symptoms in patients with rheumatoid arthritis. In a recent study patients with osteoarthritis and rheumatoid arthritis were given diaries to track their stress levels during an average week and during a week of high relational and life event stress. It was observed that during the stress week the pain scores increased for individuals with both osteoarthritis and rheumatoid arthritis (44). The subjects with rheumatoid arthritis also had elevated IL-6 levels and an increased CD4/CD8 ratio which is known to be associated with increased inflammation in these individuals. It is possible that the disordered cortisol, androgen and estrogen metabolism that occurs in plasma and joint fluid of patients with rheumatoid arthritis may be involved in further stimulating IL-6 production in these individuals (45,46).

Therefore it appears that chronic stress works in concert with anxiety, poor health behaviors, poor sleep quality, somatic complaints, depressive symptoms and inflammatory cytokines to accelerate aging and disease formation (Figure 6). All of these factors form important spokes in the disease wheel. They can individually produce physiologic dysfunction or by interacting with any of the other spokes in a non-linear process can influence disease processes. The less resilient the individual, the greater influence chronic stress will exert on disease formation.

A series of circles will be used to summarize this review (Figure 7). Inflammation, aging and disease form the perimeter of the circles and inside of it are stress, health behaviors and important intermediate health risk factors like obesity and depression. The latter circle is related to the type and quality of our relationships and emotional assets which are greatly influenced by the strength of our sense of meaning and genomic restrictions. The issue of our ascribing different and highly individualized meaning to events in our lives may be partly responsible for the different effects that a standardized stressor exerts on us as well as offering some insight into the placebo effect. The phrase “meaning response” might be a better designation than placebo for this powerful influence on our physiology (47). The expanding literature on spirituality and health also buttresses this concept. A wealth of information is likely to be published over the next several years on the relationship between chronic stress, inflammation and the diseases of aging.

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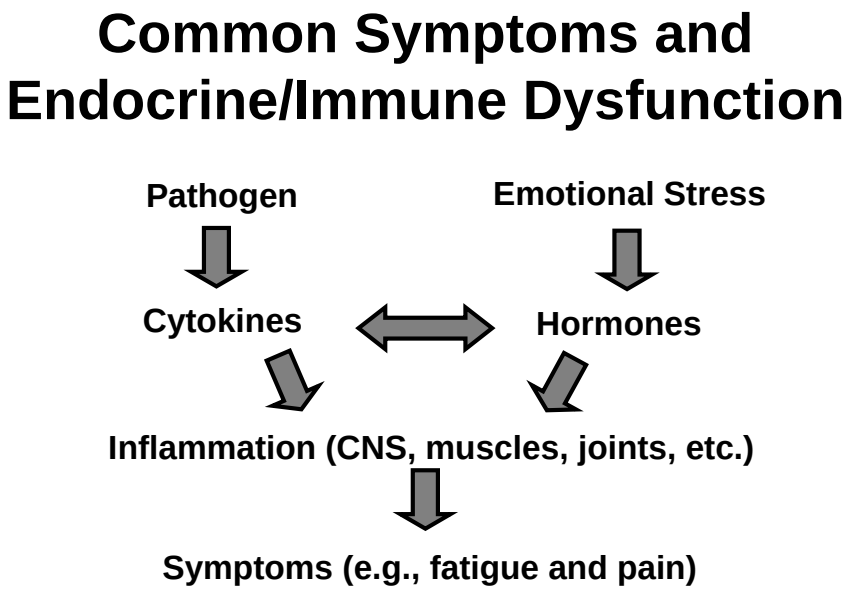
Figure Legend:

Figure 1:



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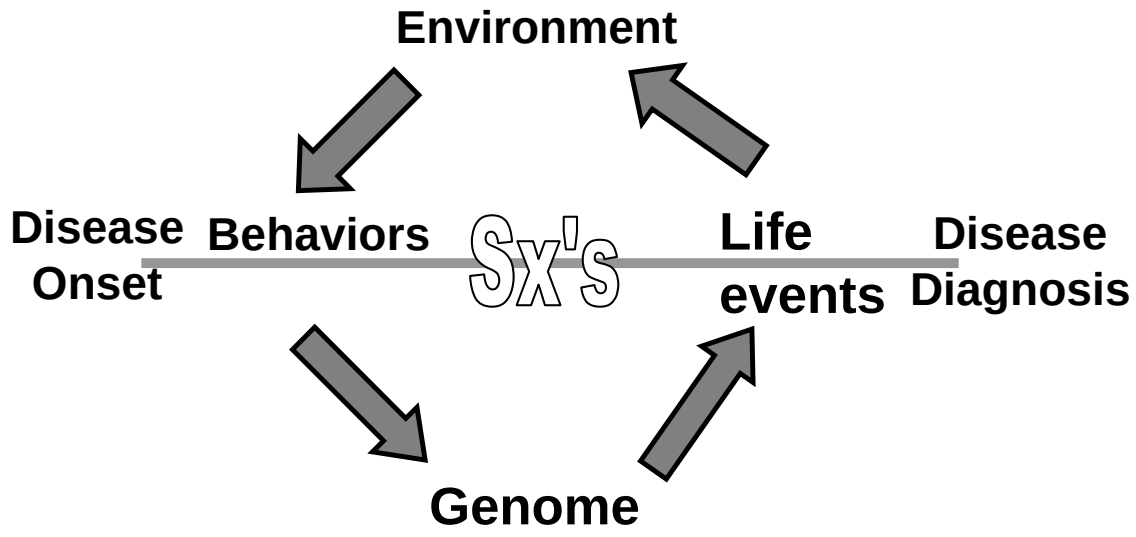
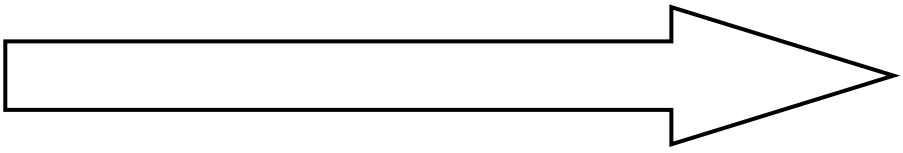


Figure 3:

PNI and Disease Pathogenesis

	Anger +	Smoking +	Depression +	Divorce
Stress	3	6	9	10
BP	100/70	120/75	135/80	**140/90**
Weight	190	190	**220**	**240**
Glucose	70	80	95	100
Coronary Lesion	-	+	++	+++

Years 

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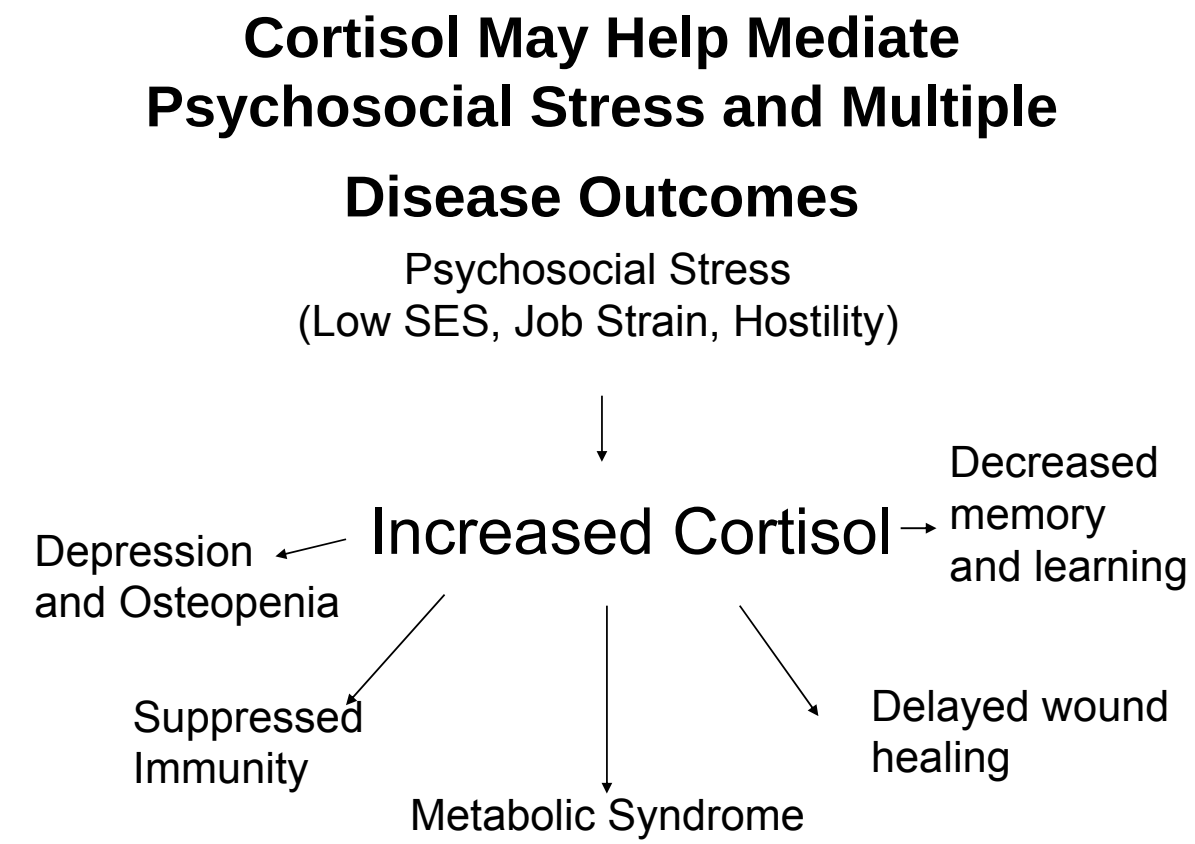

Figure 5: