Psychoneuroimmunoendocrinology

Review and Commentary

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Psychoneuroimmunoendocrinology describes the unity of mental, neurological, hormonal and immunological functions, addressing the impact of cognitive images of the mind (whatever its elusive definition) on the central nervous, endocrine and immune systems. It encompasses biofeedback and voluntary controls, impacts on physiology of thought and beliefs, past and present stress, placebos, social relationships and "energy medicine." This column highlights cogent studies from these arenas regarding holistic medicine in the new millennium.

Negative Emotions and Proinflammatory Cytokines

Negative affect and lack of supportive interpersonal relationships loom large in the picture of modulation of immune dysregulation. The latter may be one core mechanism for a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type II diabetes, certain cancers, and frailty and functional decline. Production of proinflammatory cytokines that influence these and other conditions can be stimulated directly by negative emotions. The ability to unwind after a stressful encounter down-regulates the total stress burden. Prolonged intrusive ruminations following a stressful trauma appear to provide one avenue for persistent immune downregulation including reduced NK cell activity. Higher salivary immune responses are associated with days of more positive mood. Higher social support is robustly associated with higher NK cell activity and mitogenic leukocyte responsiveness in those under stress, whereas chronically abrasive close personal relationships provoke persistent immune downregulation. Differences in perceptions to the same event provoke different endocrine and immune responses. Benefits of disclosure-based interventions vary depending on the degree to which subjects become emotionally and cognitively involved in the process, reorganize the meaning of the traumatic event, and reduce avoidance of the issue.


COMMENT: Several seminal ideas are presented here and are italicized above. This is the distilled wisdom of Janice Kiecolt-Glaser, premier researcher in the field of stress. To re-emphasize: Negative emotions stimulate proinflammatory cytokines. Inflammation is a response significantly aggravated by intense prolonged negative emotions. Which should we consider negative? One would list anger and rage, sadness and grief, and fear and anxiety. Attitudes determine our perception of the meaning of a given event, explaining the differences between subjects. And attitudes can be modified. Kiecolt-Glaser also coherently adds a therapeutic connection: the disclosure-based intervention, especially as proposed by James Pennebaker, can work extremely well, especially in situations in which the subject becomes emotionally and cognitively involved. While the practitioner cannot write a prescription for that involvement, a strong practitioner-patient relationship goes a long way in entraining a greater depth of response.

Stress and Inflammation

Molecular and biochemical bases for central nervous system-immune interactions include immune cytokines which activate immune function and also recruit central stress-responsive neurotransmitter systems in the modulation of the immune response and in the activation of adaptive behaviors after injury or inflammation. Peripherally generated cytokines, such as Interleukin-1, signal hypothalamic corticotropin releasing hormone neurons to activate pituitary-adrenal counter-regulation of inflammation through the potent antiinflammatory effects of glucocorticoids. CRH not only activates the pituitary-adrenal axis but also sets in motion a coordinated series of behavioral and physiologic responses in which the CNS coordinates both behavioral and immunologic adaptation during stressful situations. The pathophysiologic perturbation of this feedback loop, through various mechanisms, results in the development of inflammatory syndromes, such as rheumatoid arthritis and behavioral syndromes such as depression. Thus, diseases characterized by both inflammatory and emotional disturbances may derive from common alterations in specific CNS pathways (e.g. the CRH system). In addition, disruptions of this communication by genetic, infectious, toxic, or pharmacological means can influence the susceptibility to disorders associated with both behavioral and inflammatory components and potentially alter their natural history.


COMMENT: These concepts suggest that neuropharmacological agents that stimulate hypothalamic CRH might potentially be adjunctive therapy for illnesses traditionally viewed as inflammatory or autoimmune. Another way of looking at potential interventions would be to look at the modulating and normalizing effects of cultivating positive attitudes, and participating in inner disciplines such as meditation, mindfulness meditation, and Qi gong.

Immunity and Stress

Meta-analysis of stress/immunity literature showed a very significant inverse relation of stress to immune function including decreased proliferative response to mitogens (p<.001); natural killer (NK) cell activity (p<.001); numbers of WBCs (p<.001) and immunoglobulins IgA and IgM (p<.01, p<.001). Stress of interpersonal events was significantly more important than stress of nonsocial events.


COMMENT: I include this brief abstract mainly because of the authors' conclusion that the greatest stress came from issues surrounding interpersonal relations. The Fetzer Foundation has for some years taken as a major emphasis the funding of studies in Relationship-Centered Care. The importance of such research is emphasized in this meta-analysis. When patients manage to clarify, positivize and enhance their social relationships, immune-related processes including autoimmunity and immune-resistance-related phenomena tend to be more manageable.
Stress and Anti-inflammatory Signals

Of 50 healthy adults, parents of cancer patients experienced more psychological stress than parents of healthy children (p<0.05) and had flatter diurnal slopes of cortisol secretion, primarily because of reduced output during the morning hours (p<0.01). Chronic stress also impaired the immune system's response to anti-inflammatory signals: the capacity of a synthetic glucocorticoid hormone to suppress in vitro production of the pro-inflammatory cytokine interleukin-6 was diminished among parents of cancer patients (p<0.05).


COMMENT: Here is another piece of the puzzle. These data suggest a novel pathway by which chronic stress might alter the course of inflammatory disease. Chronic stress appeared to impair the immune system's capacity to respond to hormonal signals that would terminate inflammation. The stressed body misses and thus fails to respond to anti-inflammatory signals.

Inflammation and Stress

In response to psychological or certain physiological stressors, an inflammatory process may occur through release of neuropeptides (especially substance P or other inflammatory mediators) from sensory nerves and the activation of mast cells or other inflammatory cells. Central neuropeptides, including corticotropin releasing factor and perhaps substance P as well, initiate a systemic stress mobilization response by activating the sympathetic nervous system, hypothalamic-pituitary axis, and the renin-angiotensin system, thus releasing stress hormones (catecholamines, corticosteroids, growth hormone, glucagon, and renin) which, together with cytokines induced by stress, initiate the acute phase response and the induction of acute phase proteins, essential mediators of inflammation. CNS norepinephrine may also induce the acute phase response by macrophage activation and cytokine release. Increase in lipids with stress may also be a factor in macrophage activation and lipopolysaccharide release which may induce cytokines from hepatic Kupffer cells, subsequent to an enhanced absorption from the gastrointestinal tract during psychological stress. The brain is capable of initiating or inhibiting the inflammatory process. The inflammatory response is contained within the psychological stress response which was a later development in human evolution. Moreover, the same neuropeptides (i.e., CRF and possibly substance P) mediate both stress and inflammation. Cytokines evoked by either a stress or inflammatory response may utilize similar somatosensory pathways to signal the brain. Repeated episodes of acute or chronic psychogenic stress may produce chronic inflammatory changes which may result in atherosclerosis in the arteries or chronic inflammatory changes in other organs as well.


COMMENT: As delineated in this summary, derangement of immune responses related to poor management of stressors participates in altering the inflammatory responses which play major roles in atherosclerotic disease. Many theorists now think that the final event in rupture of arterial plaques is related to an acute inflammatory response. This may explain the relation of acute myocardial infarction to acute outbursts of anger. It is probably true that inflammatory attitudes are more than metaphorically related to chemical inflammatory responses in the body.

Inflammatory Dermatoses and the Mind

It is only recently that Western physicians are rediscovering the link between thought and health. The spectrum of causative factors in inflammatory dermatoses are often multifactorial. Stress and negative thoughts are major factors in dermatological conditions. This article delineates some basic information on the ways that thoughts affect health. Practical methods of intervention include meditation, journal writing, affirmations, prayer, biofeedback, and hypnosis.


COMMENT: This editorial commentary points out practical and effective interventions in inflammatory skin conditions. This is a piece to mind-body interventions. Holistic practitioners often come to the awareness of the potential for non-pharmacological interventions not of a sense of failure or suboptimal response from pharmacological approaches. In this dermatological journal, the authors appeal not to an alternative approach, but to an integrated holistic approach, avoiding the either/or dichotomy. My own bias is to use psycho-social-spiritual interventions first and pharmacological ones last, but I support any integrated combination of the two. And we need to remember that the uncomfortable truth that the most common awareness of the need for a fresh look at disease management and the importance of lifestyle comes out of a patient crisis.

Infections, Immunity and Stress

Immune function is mediated by the release of cytokines (nonantibody messenger molecules) from a variety of immune and endothelial cells. Cytokine release stimulates the inflammatory response, induced by hormonal changes elicited following activation of the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes. The experience of stress inhibits natural killer cell responsiveness, T-cell responses and antibody responses in vivo and in vitro. Studies showing little effect on actual disease incidence have been done mainly in healthy young volunteers whose immune systems have much greater levels of reserve. Wound healing is compromised by stress, adding to post-surgical expense. Susceptibility to cold viruses is consistently found to be much greater in stressed populations, and most HIV studies link stress with a diminished prognosis. Stress is also associated with prolonged recovery from infections. Lifestyle changes, including the broadening of interpersonal relational interactions (social and spiritual groups, having a confidant, engagement with friends) enhances greater resistance and immune responsiveness.


COMMENT: Several well-known researchers jointly published this review. The experience of stress significantly distorts normal immunologically mediated inflammatory responses. The stressors inducing these responses may be physical, but in our relatively controlled society are mainly psycho-social. One's own inner high-level psychic demands and social isolation are both implicit stressors which induce excessive inflammatory responses. Practitioners taking a holistic view of medical practice including recognition of these powerful psychological and social influences, will usually find better outcomes utilizing a multidisciplinary approach.
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**Helicobacter pylori and Stress**

The oral cavity is suspected to be involved in the transmission of *H. pylori*, a cause of gastritis and ulcers. Saliva was collected from 17 undergraduate volunteers before, during, and after exposure to a stressful video showing graphic surgical procedures. During stressor exposure, participants reported increased state anxiety, and stroke volume rose and cardiac rate fell. The stressor induced a marked increase in salivary levels of mucosal adhesion molecule for *H. pylori*, and saliva-mediated adherence of *H. pylori* to mucosal surfaces in vitro. As expected, the mucosal adhesion molecule levels correlated with the adherence of *H. pylori* (p<.05).

**COMMENT:** This study demonstrated a direct link between stress-mediated biochemical changes and altered host-*H. pylori* interactions. *H. pylori* appears to play a role in gastric and duodenal ulcers and its route of entry is suspected to be via the buccal cavity. If studies of the adherence of *H. pylori* to the mucosal gastric surface demonstrate the same characteristic relationship to stress as shown here, the suspected relationship of stress to ulcer disease, denigrated by many conventional authorities, might find a new lease on life. Stress would then become a contributing factor to ulcers by means of an entirely new pathway: greater facilitation of *H. pylori* infection.

**Mononucleosis and Psychosocial Factors**

Twenty-eight hospitalized and 22 outpatient students ill with mononucleosis were psychologically evaluated. In men, significant correlations were present with a broken love relationship in the prior month (p<.05) and dissatisfaction with the school year (p<.05). In women, associated factors were consideration of withdrawal from school in the prior month (p<.05), seeing a personal counselor in the prior month (p<.01) and low level of her father's education (p<.05). The most significant correlation on the California Psychological Inventory was in the intellectual effectiveness scale in women (p<.025).

**COMMENT:** Immunological susceptibility is related to psychosocial upheaval. It may be more precise to say that it is the interpretation of the meaning of the incident of upheaval which bears the strongest relationship to susceptibility. It is in the parsing of these two descriptions that the belief system, attitudinal worldview and the balance of inner vs. outer locus of control become quintessential. In popular vernacular, Louis Harris' "I'm O.K., You're O.K." outlook stemming from a positive attitude about oneself and the world seems to invite the optimum responsiveness of the immune system in regard to overcome inflammatory responses and susceptibility to infection.

**Acquired Immunodeficiency Syndrome and Emotional Support**

Forty-nine Swedish, male, hemophilic, HIV-infected men were identified in 1986. After personal interview, an "availability of attachment" score was calculated based on the strength of their social support systems. Followed 4 years, low-sociably-supported subjects had significantly more rapid deterioration in their CD4 counts vs. high-sociably-supported subjects (p=.0001).

**COMMENT:** Social relationships have a bearing on both the incidence and course of disease. In these HIV-positive men, lack of social support predisposed to more rapid deterioration of their immune resistance. The numbers of social relationships, the depth of those relationships, and the frequency of contacts within relationships are factors which are related to the predictability of deterioration in infectious and inflammatory diseases.

**Colds and Social Support**

Two-hundred-seventy-six healthy volunteers age 18-55 were interviewed and followed for susceptibility to cold viruses. The subjects were separated by history into those with 1-3 types of social ties v. those with >6 types of social ties. Each used nasal drops containing one of two rhinoviruses. Presence of a cold was assessed by mucus production, mucociliary clearance and amount of viral replication. Over the period of observation, those with <3 types of social connections had a relative risk for infection on exposure of 4.2 vs. those with >6 types of social connections (p<.01). They had greater susceptibility to colds, increased mucus secretion, decreased ciliary clearing of nasal membranes and shed more virus. These significant relationships were unaffected by a wide range of possible variables. Smoking, poor sleep quality, abstinence from alcohol, low vitamin C intake, elevated catecholamines and introversion, also contributed to susceptibility. The 12 types of social ties were to spouse, parent, co-worker, friend, teacher, member of social group, children, etc.

**COMMENT:** The more diverse the social network, the greater the immune resistance. Other studies show that the intensity and duration of upper respiratory viral illnesses is greater in the socially isolated and more highly stressed. None of this research negates the importance of the strength of the bacterial or viral inoculum. The strength of the host is the greater factor, however, than the inoculum. Remember the vignette in which Louis Pasteur, discoverer of microbial diseases, is said to have uttered on his deathbed, "Alas, [Claude] Bernard is right, the "territory" [strength of the host] is everything."

**The Stress of Caregiving in Chronic Illness**

Sixty-nine spousal caregivers of dementia relatives >5 years duration were contrasted to 69 sociodemographically matched controls. Caregivers had significantly increased incidence of infectious illness and depression, significantly less sleep (all p<.001) and significant decreases in three measures of cellular immunity. Blastogenesis in response to phytohemagglutinin and concanavalin A challenge was significantly lower in caregivers in comparison with controls (p<.01). The progressive immunological changes over time were significant at p<.001.

**COMMENT:** The stress of being a principal caregiver for a demented person results in susceptibility to infectious illness. Leucocyte responsiveness to immune challenge was blunted and progressively worsened with time.

**Infections in Schizophrenia Caregivers**

A nurse interviewer, blind to the patient's symptoms, caregiver burden, and psychosocial status, administered the Health Review questionnaire to 70 schizophrenia caregivers. A second interviewer, blind to caregiver health status and patient symptoms, assessed caregiver resources (e.g., active coping and social support), vulnerabilities (e.g., anger expression and...
passive coping) and burden. Concurrently, independent patient raters, blind to caregiver health and psychosocial status, assessed caregiver stressors. Other appropriate psychological assessment instruments evaluated the severity of positive (e.g., hallucinations and delusions) and negative (e.g., anhedonia and asociality) symptoms. Measures of stressors, resources, and vulnerability factors accounted for 29% of the variance in infectious illness. Positive patient symptoms and dissatisfaction with social support were highly predictive of infectious illness episodes. Caregivers whose stress ratings placed them in the uppermost quartile were at four times the risk for infectious illness vs. those in the lowest quartile.


COMMENT: Schizophrenia caregiving is another clinical situation which is highly stressful and in this study, schizophrenia caregiver stress levels were highly predictive of susceptibility to infectious illness. Although not part of this research, practitioners aware of this relationship would do well to assist caregivers in highly stressful circumstances (managing schizophrenics, Alzheimer's patients and other highly asocial patients) in recognizing their stressful circumstances, arranging for respite intervals, and using other lifestyle tools (better nutrition, exercise, meditation, positive social contacts) to minimize the downside effects of the unavoidable stressor experience.

Robert Anderson is a retired family physician whose practice took a holistic turn as decades passed. He has authored five major books, Stress Power!, Wellness Medicine, The Complete Self-Care Guide to Holistic Medicine (co-author), Clinician's Guide to Holistic Medicine (McGraw Hill, 2001), and The Scientific Basis for Holistic Medicine, (6th edition 2004), available from American Health Press, holos@nw.net. Anderson was the founding president of the American Board of Holistic Medicine, past president of the AHMA, former Assistant Clinical Professor of Family Medicine at the University of Washington and is currently an Adjunct Instructor in Family Medicine at Bastyr University.