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 ($p<0.05$).

Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol* 2002 Nov; 21(6):531-41

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.

Black PH. Stress and the inflammatory response: A review of neurogenic inflammation. *Brain Behav Immun* 2002 Dec; 16(6):622-53

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.

Bilkis MR, Mark KA. Mind-body medicine. Practical applications in dermatology. *Arch Dermatol* 1998 Nov; 134(11):1437-41

COMMENT: This editorial commentary points out practical and effective interventions in inflammatory skin conditions. This is a paean to mind-body interventions. Holistic practitioners often come to the awareness of the potential for non-pharmacological interventions out 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.

Glaser R, Rabin B, Chesney M et al. Stress-induced immunomodulation. Implications for infectious diseases? *JAMA* 1999 Jun 23/30; 281(24):2268-70

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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