Stress, Chronic Infection, and the Immune System

Parental Affection
The development of infants in a foundling home raised in a hygienic environment with a nurse/infant ratio of 1:8, permitting only feedings and diaper changes with contact limited to the brief feeding times, was compared with that of infants of parents incarcerated in a prison in which mothers had extended contact time each day with their infants. Mortality from infection by two years of age was 37% and 0 %, respectively.


Comment: We do not commonly see instances of marasmus in today's medical scene. One hundred years ago, pediatric death from lack of stimulation, touching, and stroking in foundling homes was not uncommonly heralded by onset of a variety of infections. Although no statistical analysis is presented here, the significance is unquestionably valid. If there was ever an unassailable appeal for the importance of relationship and human connections in health, this is it.

Stress, Cellular and Humoral Immunity
This was a meta-analysis of over 300 studies on stress from 1960 to 2001, encompassing 18,841 subjects, describing a relationship between psychological stress and parameters of the immune system in human participants. Acute stressors (lasting minutes) were associated with potentially adaptive upregulation of some parameters of natural immunity and downregulation of some functions of specific immunity. These included acute stress in which the immune system battles infections and other physical traumas. Brief situational stressors (such as examinations) tended to suppress cellular immunity while preserving humoral immunity. Long-term stress fell into 3 categories: challenges that have a limited scope and some end point; long-term stresses that have an unlimited or infinite scope; and remote stresses stemming from untoward past experience in childhood or early adult life with unresolved consequences. Chronic stressors were associated with suppression of both cellular and humoral immunity. Effects of event sequences varied according to the kind of event (trauma vs. loss). In some cases, physical vulnerability as a function of age or disease also increased vulnerability to immune change during stressors.


Comment: The authors conclude that the sources of stress may be acute, chronic, and ongoing, or stemming from unresolved psychological or physical traumas from childhood or early adulthood. The latter source often hovers in the unconscious for years or decades. So the immune dysregulation is then chronic or recurrent, not lending itself to final solution until the early life traumas come to light. This occurs usually in the supportive doctor-patient relationship that has been cultivated with empathy and patience over long periods of time.

Acquired Immunodeficiency Syndrome (AIDS) and Emotional Support
Forty-nine Swedish, male, hemophiliac, HIV-infected men were identified in 1986. After personal interview, an “availability of attachment” score was calculated based on their social support systems. Followed 4 years, low-social-support subjects had significantly more rapid deterioration in their CD4 counts vs. high-social-support subjects (p = .0001).

Comment: Social relationships have a bearing on both the incidence and course of infectious disease. Depressed and less socially attached persons are more vulnerable to passing viruses and bacterial invaders. Pediatric carriers of known pathogens can remain in healthy states for months at a time without succumbing to clinical illness. Positive family climates are correlated with better pediatric immune resistance which allows this resistant picture to be maintained.

Colds and Social Support
Two hundred seventy-six healthy volunteers aged 18 to 55 were interviewed and followed for susceptibility to cold viruses. The subjects were separated by history into those with one to three types of social ties versus those with more than six types of social ties. All subjects deliberately sprayed themselves with 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 one to three types of social connections had a relative risk for infection on exposure of 4.2 compared with those with over six types of social connections. They had greater susceptibility to colds, increased mucus secretion, decreased ciliary clearing of nasal membranes, and shed more viruses. These significant relationships (p < .01) 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, coworker, friend, member of a social group, etc.

Comment: The more diverse the social network, the greater the immune resistance. Enormous numbers of the population have limited social ties. This issue has become worse with many persons living alone and spending time with electronic devices (televisions, computer screens, and electronic communication). We as a society may be shooting ourselves in the foot by not giving oncoming generations the skills to be socially integrated and involved.

Immunity and Stress
This is a review of numerous studies demonstrating that stress is strongly related to some aspect of immunoincompetence and/or an increase in infection and illness behavior. The incidence of influenza has been found to be higher in chaotic and rigid families compared with unstressed (balanced) families. Higher antibody levels (an indicator of maladaptive immune response) to common viruses (Epstein-Barr virus and herpes 1 virus) have been shown in recently separated women, separated and divorced men, Alzheimer’s caregivers, Pennsylvania residents near Three Mile Island, and depressed subjects. Increase in negative mood and decrease in positive mood was shown in 34/37 subjects just before they became febrile after being deliberately exposed to a bacterial inoculum. Cohen S, Williamson CM. Stress and infectious disease in humans. Psychol Bull. 1991 Jan;109(1):5-24.

Comment: This is one of numerous studies correlating stress with some aspect of immunoincompetence and/or an increase in infection. While superb diet and regular physical exercise combine to enhance immune activity and defenses, mind-body relationships also exert pervasive influences on susceptibility.

Other stresses shown to compromise immunity include the stress of sleep deprivation. Following 48 hours of sleep deprivation, 12 young male volunteers showed marked reductions of DNA synthesis after stimulation with phytohemagglutinin. Preexposure levels were regained 5 days after terminating the vigil. No changes were noted in granulocyte adherence or alkaline phosphatase activity. The results suggest that sleep deprivation may decrease cell-mediated immune reactions and thereby impair some aspects of host defense. Palmblad J et al. Lymphocyte and granulocyte reactions during sleep deprivation. Psychosom Med. 1979 Jun;41(4):273–278.

Comment: It is a common experience to feel poorly in a generic way after one or more nights of poor sleep. It is also surprisingly common in my own personal experience to become ill with an upper respiratory virus under the same circumstances. Exposure to the acute stress of a night or two of poor sleep superimposed on chronic stresses of long work hours, marital discord, teen-age maladaptive behavior in offspring, rejection by co-workers, etc., provides the seedbed for susceptibility to infection(s).

Two equal-sized groups preassigned by Minnesota Multiphasic Personality Inventory scoring to “high distress” or “low distress” cohorts were checked for nucleoid migration of lymphocytes in DNA repair after brief irradiation exposure of 100 rads. The low-distress group scored 100 vs. a high-distress group scoring 85, a statistically significant improved response (p = .026). Kiecolt-Glaser JK et al. Distress and DNA repair in human lymphocytes. J Behav Med. 1985 Dec;8:311–320.

Comment: The Glasers at Ohio State University have made seminal contributions to the studies of stress and illness over the past three decades. This study of persons exhibiting high distress levels found deterioration in immune lymphocyte function under exposure of brief radiation exposure at levels manyfold lower than CT scan radiation exposure. Most practitioners do not even think about the immune effects following CT exposure and the downstream effects on immunity and inflammation.

38 married women and 38 women separated/divorced for less than one year were studied. Those separated/divorced for less than one year had depressed immunity. Four measures of immune function measured included natural killer assay, percentage of T-lymphocytes and T4/T8 ratio, response to mitogenic challenge with PHA and ConA, and levels of Epstein-Barr virus capsid antigen.
Subjects completed five psychological instruments. Marital arguments and poor marital quality were significantly inversely correlated with depressed ConA response (p < .004) and PHA response (p < .05). T suppressor cells were inversely correlated with marital quality (p < .05). Separated/divorced women had lower natural killer cell counts (p < .05), more depression (p < .001), and higher EBV VCA levels (p < .05) compared with married women.


Comment: Implications of this 20-year-old study remain valid. Studies demonstrating the benefits of social contact, involvement, and support continue to be published. Human beings tend to function with a better quality and length of life when in close relationships with other human beings.

Stress events that have been shown to lead to immune system changes include divorce, unemployment, anxiety, loneliness, sleep deprivation, marital unhappiness, overcrowding, high-intensity sound, bereavement, administration of epinephrine and norepinephrine, corticosteroids, academic examinations, and mental arithmetic testing. The amygdala and hypothalamus have 40 times more neuropeptide receptors than any other parts of the brain. Behavioral interventions that have been demonstrated to enhance immunity include clinical biofeedback, meditation, autogenic training, Jacobsen's progressive relaxation, hypnosis, general relaxation, behavior modification, and visualization and imagery techniques.


Comment: This is Ken Pelletier's summation of years of research into mind-body connections. Also significant is his mention of the variety of approaches by which stressed persons can reverse the blunted responsiveness of the immune system that almost inevitably follows exposure to the three sources of stress mentioned above.

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


Comment: Herbert and Cohen here show that interpersonal stress ranks much higher on the scale of importance than nonsocial events such as hurricanes, earthquakes, and vehicle breakdowns. The immune system simply does not like unmanaged interpersonal stress. Would that we could write simple prescriptions to reverse this issue for our patients.

Stress was induced in laboratory mice by restraining the animals. The cellular response to local herpes simplex virus was determined at baseline. Restraint stress reduced cellular production from 7.9 to 3.2 × 10^6 cells and 6.9 to 3.9 × 10^6 cells in two experiments (p < .02). Treatment with nadolol failed to restore the cellular production decreased by stress. Treatment with RU486, a glucocorticoid receptor antagonist, partially reversed the stress-induced diminution of cellular immune response to local herpesvirus infection, and treatment with nadolol, a peripherally acting alpha-adrenergic antagonist, with RU486 completely reversed the restraint stress-induced suppression of HSV-specific cytotoxic lymphocyte activation (p < .01).


Comment: These findings demonstrated that corticosterone and catecholamine-mediated mechanisms are both involved in the stress-induced suppression of antiviral cellular immunity. Both are, of course, common pathways for endocrinologic expression of stress-related exposure. Humans do have at least one modulating option, related to how threatening the stress is perceived to be. The quality of equanimity greatly modifies the perception of how stressful a given event may be. In my experience, equanimity is usually the result of years of self-reflection and skill development.

Ninety-five randomly selected 18-year-olds from a pool of 583 consenting first-year West Point cadets had blood
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drawn at registration into the academy program, at the end of the first 6 weeks of cadet basic training, following winter holidays on return to the academy, and during second-year final examinations. A battery of 5 psychological instruments was completed and repeated one year later. Antibody levels remained essentially unchanged until the fourth blood drawing at final examination time, at which time there was a very significant rise in Epstein-Barr virus titers (p < .001), with no significant increases in HSV-1 and HHV-6 antibody levels. There were also no significant correlations with psychological data from the completed test instruments.

Comment: The academic stress of final examinations, but not the physical and psychosocial stress of basic training, significantly reactivated latent mononucleosis virus activity in these service cadets, but not that of HSV-1 or HHV-6. These 3 herpesviruses, causing mononucleosis, gingivostomatitis, and exanthem subitum, respectively, remain in a steady state held at bay by cell-mediated immunity. Reactivation at final examination time, implying compromise of the immune system with consequent secondary rise in antibody titers, gives testimony to the intensity of the stress involved in academic competitive testing. The very significant rise in EBV antibodies confirms previous work showing this stress response of the immune system.

Immunity, Stress, and Health

Sixty-nine spousal caregivers of patients with dementia of over five years’ duration were contrasted to 69 sociodemographically matched controls. Caregivers had significantly increased incidences of depression and infectious illness, significantly less sleep (p < .001), and significant decreases in three measures of cellular immunity. Blastogenesis in response to PHA and ConA challenge was significantly higher in controls than caregivers (p < .01). The progressive immunological changes over time were significant at p < .001.

Comment: Caregivers of demented relatives have become one of the classical models for stress research. This social activity taxes the capabilities of even the strongest and healthiest balanced spouse. The management of caregiving situations for the demented begs for better solutions by the medical community and society.

Immunological Memory and Social Defeat

Immunological memory (MEM) development is affected by stress-induced neuroendocrine mediators. In this study, the experience of social disruption stress (SDR) prior to a primary influenza viral infection enhanced the frequency and function of the T cell memory pool. Socially stressed mice had a significantly enlarged population of CD8+ T cells specific for the immunodominant A/PR/8/34 virus in lung and spleen tissues 6 to 12 wks after primary infection (resting memory). Moreover, during resting memory, SDR-MEM mice responded with an enhanced delayed-type hypersensitivity response, and more IFN-gamma-producing CD4+ T cells were detected after ex vivo stimulation. When mice were rechallenged with A/PR/8/34 virus, SDR-MEM mice terminated viral gene expression significantly earlier than MEM mice and generated a greater CD8+ T cell response in lung parenchyma. This enhancement was specific to the T cell response. SDR-MEM mice had significantly attenuated anti-influenza IgG titers during resting memory.

Comment: This mice study demonstrates that the experience of repeated social defeat prior to a primary viral infection significantly enhances virus-specific memory via augmentation of memory T cell populations, and suggests that social stressors should be carefully considered in the analysis of implications on antiviral immunity. We assume that the human may behave in a fashion similar to our experimental mice.

Immunity, Inflammation, and Interleukin-6

In 211 middle-aged men and women undertaking stressful tasks, natural killer (NK) cell counts increased and were positively associated with heart rate variability responses independent of age, sex, socioeconomic status, smoking, and change in hematocrit. Heart rate 45 minutes poststress was positively associated with plasma IL-6, and with TNF-α changes from baseline, independently of covariates.


Robert Anderson is a family physician who has authored several major books: Stress Power!, Wellness Medicine, Clinician’s Guide to Holistic Medicine, and The Scientific Basis for Holistic Medicine. Anderson founded the American Board of Integrative Holistic Medicine, is a past president of the AHMA, past assistant clinical professor of family medicine at the University of Washington, and present adjunct instructor in the Art of Primary Care at Bastyr University.