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Rider MS et al. Effect of immune system imagery on secretory IgA. Biofeedback Self Regul 1990 Dec; 16(4):317-33

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Forty-one adults completed 8 psychological instruments measuring mood, stress, health status and phagocytic activation capacity - the respiratory burst or capacity to utilize O2 for synthesis of bactericidal substances. A significant correlation between high stress and low phagocytic activation capacity was apparent (p<0.05). Then 16 subjects scoring high in stress and low in immunity were randomized to either a control group or an experimental group whose members completed a psychological instrument to assess baseline levels of relaxation which was then confirmed by biofeedback EMG and thermal readings. Treatment subjects underwent 7-14 one-hour biofeedback-assisted tense-relax training sessions b.i.w. augmented by home practice until finger temperatures >95°F and EMG frontalis readings <1.2 µv.

The treatment group increased phagocytic activation capacity from 66 to 109 v. a fall from 83 to 79 in controls (2p<0.0003). There were also significant improvements in anxiety (p<.04), family stress (p<.05), family coping (p<.05), work stress (p<.05) and personal coping (p<.001). Overall levels of coping were significantly improved compared to controls (p<.001).


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The Immune System and Mind Function

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.

Psychoneuroimmunoendocrinology Review and Commentary
by Robert A. Anderson, MD
614 Daniels Drive NE
East Wenatchee, Washington 98802 USA

The Immune System and Mind Function

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These Things Are Stressful; These Things Help Us Manage the Stress
Stress events which have been shown to lead to immune system changes include divorce, unemployment, anxiety, loneliness, sleep deprivation, marital unhappiness, overcrowding, high intensity sound, bereavement (death of spouse and wives with terminal cancer), 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 which 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 a Kenneth Pelletier summary of the major sources of stress in our society as shown in research, as well as the major techniques which assist patients (and ourselves, of course) in managing the effects of the stress. It has been my experience that meditators and those regularly practicing relaxation techniques have a greatly elevated tolerance for stress and a markedly elevated threshold required for them to begin to experience untoward physical, mental and emotional results.

More on Examinations
Salivary IgA determinations were done in 15 healthy undergraduates five days before exams, during exams and...
fourteen days following their last final exam. sIgA levels were lower during exams (p<.0001). Students reporting more social support at the pre-exam time had consistently higher sIgA levels than their peers with less social support (p<.05).


**COMMENT**: This is consistent with the theory that social support enhances health. In this instance, students with greater social support began the vulnerable exam time with higher sIgA levels. The social support literature indicates that both numbers of persons in one's social support network as well as depth of relationship both auger for benefits in being more resistant to stress and its effects.

**The Stress/Immunity Theory has its Critics**

In this meta-analysis of 24 stress studies and ten relaxation studies vis-a-vis immunity, objective measures of immunity were insignificantly related to stress and relaxation with the exception of greater interleukin-2 receptor expression on lymphocytes and antibody titers against Epstein Barr virus (p<.0001).


**COMMENT**: There is never 100% agreement on anything in medicine. And just to prove my unbiased nature, I report here that not all researchers agree that the effects are as ubiquitous as most of their colleagues believe. Even so, two laboratory measures were altered by stress in this meta-analysis, so we are discussing the degree to which stress causes negative effects. This study did not measure or analyze psychological and mental/emotional effects.

**Another Meta-Analysis**

This 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); NK cell activity (p<.001); numbers of WBCs (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 non-social events.


**COMMENT**: In contrast to the naysayers above, this analysis found rather profound effects in immune responsiveness under stressful conditions. And I find that most researchers are in the camp of these folks. Of note as well, is the last comment that the stress of interpersonal social events was more profound that that related to non-social events. It’s “our stuff” relating to people than is the most problematic for us.

**Parachute Jumpers**

In 45 first-time parachutists, the psychological stress increased sympathetic adrenal hormones epinephrine and norepinephrine, cortisol, heart rate, respiratory rate and fear ratings (p<.001) at the time of jumping. Significant immediate increases in T-cell counts (CD4+, CD8+, CD4+ [p=.001] and CD8+ [p=.01]) and a doubling of NK^ and NK cell counts (p=.001) were found. Twenty minutes after the jump, epinephrine and norepinephrine were at baseline levels, and all immune cellular
parameters were significantly below baselines (p=.001). Cortisol returned to baseline one hour following the jump. Experienced jumpers had much smaller and mostly insignificant changes. Schedlewski M et al. Psychophysiological, neuroendocrine and cellular immune reactions under psychological stress. Neurosci Biobehav Rev 1993; 17(5):467-78

COMMENT: I must admit that I was slightly stressed just thinking about this research. I must not be all that adventuresome at my age. Experience reduced the impact of stressful experience in these jumpers, and effects were short term in the young and fit. Of note as well, but not researched here, is the great benefit of mental rehearsal in which a significant portion of the early practice of such a stressful experience can be done in the imagination. A number of years ago when on a mountain climb with a group of male friends, one of them had agreed to instruct the rest of us in the technique of ice-ax arrest on steep snow or glacial slopes. As we prepared to sleep the night before he smilingly said he taught people how to self-arrest by giving them a push when unexpected, requiring them (me!) to roll and plant the spike of the ice ax into the ice and snow. With this specter in my head I was unable to sleep at the base camp until I began to rehearse the entire maneuver in my head like still frame photography. With a few passes completing the mental rehearsal, I dropped off to sleep and performed almost flawlessly the next day.

Interferon and Interleukins in Alzheimer’s Caregivers

Natural killer (NK) cell reactions to incubation with recombinant interferon-γ or recombinant interleukin-2 were measured in 28 former and current caregivers of patients with AD and 28 matched controls. The response of both present and former Alzheimer’s caregivers was similar and was significantly suppressed compared to controls (p=.01). Higher levels of positive emotional and tangible social support were associated with higher levels of response to these two cytokines (p<.01).


COMMENT: The humoral as well as the cellular immune system is affected by stress when it is not managed well. The most alarming statistic here is that former caregivers had immune systems that were compromised to a degree equivalent to current caregivers. When the caregiving stress is over, but supplanted by the grieving for the death of the spouse, survivors should be given the opportunity for experiential stress management and relaxation training to help restore the immune system to potency.

Examinations and Skin Testing

Sixteen final-year psychology undergraduate students about to take their final examinations and 14 controls from research and administrative staff with a similar age distribution were randomly recruited to complete the 30-item Recent Perceived Stress Questionnaire and have applied to a forearm the Multitest 28, which simultaneously imprints the derris with seven delayed hypersensitivity antigens (tuberculin, tetanus, diphtheria, streptococcus, candida, Trichophyton, and proteus). Dermal indurations were read at 48 hours. Mean perceived stress score for the students was 72.7 vs. 58.5 for the controls. The stress group immune response to challenge was significantly weaker and smaller than those of the unstressed group. Other small studies have shown the disappearance and reduction of positive skin test reactions in different conditions including hypnosis, meditation and guided imagery. In one case study, guided imagery/hypnosis led to a significantly smaller induration in one arm compared to another with simultaneous application of the same dose of the challenge agent. The immune system does not exist in isolation outside the realm of the mind. And these data make some aspects of what we call science somewhat questionable.

Alzheimer’s Caregivers

The cell adhesion molecule, L-selectin (CD62L), serves a crucial role in the migration of naïve T lymphocytes and is typically shed on cell activation. Twenty Alzheimer’s caregivers, mean age 73.5 had their lymphocytes and catecholamine levels sampled at rest and in response to an acute psychological stressor. Ten of the caregivers were categorized as susceptible or “vulnerable” based on the large amount of care required by the patient relative to the amount of respite the caregiver received during the previous 6 months. At rest, vulnerable caregivers had 60% fewer L-selectin negative CD8+ T cells (CD8+CD62L-) (p=.01) but no difference in CD8+CD62L+ cells. Vulnerable caregivers also showed significantly fewer CD4+CD62L- T lymphocytes (p=.04) but no difference in CD4+CD62L+ lymphocytes. Resting plasma epinephrine levels were 44% higher in vulnerable caregivers v. nonvulnerable caregivers (p=.01). The acute stressor increased circulating levels of CD8+CD62L- and CD8+CD62L+ lymphocytes and catecholamines similarly in both groups.

Mills PJ et al. Vulnerable caregivers of patients with Alzheimer’s disease have a deficit in circulating CD62L- T lymphocytes. Psychosom Med 1999 Mar; 61(2):168-74

COMMENT: These data suggest that caregivers who are more vulnerable to the chronic stress of caregiving show a decrement in circulating CD62L-T lymphocytes, possibly by adrenomedullary activation under acute stress. The data also suggest the precise identity of the lymphocyte subset that undergoes immunological decrement during the chronic stress of caregiving. Susceptibility to a wide variety of potential invaders and toxic agents is implied for the stress caregivers.

Matriculating at West Point

Ninety-five randomly selected 18 year-olds from a pool of 583 consenting first-year West Point cadets had blood 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 EBV 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, 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 which can be
extrapolated to our entire educational system. The very significant rise in EBV antibodies confirms previous work showing this stress response of the immune system.

Caregivers for the Demented

Sixty-nine spousal caregivers of demented relatives of more than 5 years' duration were contrasted to 69 sociodemographically matched controls. Caregivers had significantly increased incidence 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) and IgG viral capsid antibodies to Epstein Barr Virus were significantly lower in caregivers (p<.05). The progressive immunological changes over time were significant at p<.001.


COMMENT: It has been previously established that great stress is attendant to caregiving for demented persons. The constant nature of tending to have little respite from the demands of such caregiving is thought to be a significant contributor to the global definition of the stress involved. There is also some preliminary data to suggest that those who have previously undergone relaxation training of some sort (biofeedback, meditation, progressive relaxation, autogenics, etc.) tolerate the caregiving with less erosion of health including the immune system.

Unavoidable Stress

One-hundred five adult men were randomly exposed to controllable or uncontrollable stress (noise), and compared to no-noise controls. NK cell activity was determined before and after each of three 20-minute exposures to noise, and 24 and 72 hours following the last exposure. The subjects were randomized to group 1) in which they could turn the noise off; group 2) in which they could not escape the noise but thought their efforts would do so; 3) in which they were told to tolerate the noise; and 4) in which they spent an equivalent time not exposed to noise. No-noise controls and subjects who perceived that they had control over the noise showed no reduction in NK cell activity. Subjects believing they had no control over a 20-minute exposure to noise (group 3) had an immediate reduction in NK activity which persisted up to 72 hours and was significantly greater than in the controllable-noise group and the no-noise group (p<.001).


COMMENT: High desire to control the noise stress enhanced the negative impact of uncontrollable noise on NK activity. The need to control appeared to be a negative factor on outcome.

Additionally, the group believing they had no control over the stressful noise had a profound reduction in NK cell activity lasting up to three days. People in our society who are burdened with hopeless and helpless feelings can be expected to have compromised NK immunity.

Dermatomyositis

This is a case history of a dermatomyositis patient treated with Transcendental Meditation and visual imagery without drugs for 294 days during which the patient recovered, a low-

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**OPTIMAL NUTRITIONAL SUPPORT**
Mind Function

probability event without conventional therapy. Regression analysis of periodic measures of arm strength, rash, and pain vis-a-vis application of mind-body treatments found significance for both Transcendental Meditation (p=0.02 to 0.001) and visual imagery (p=0.02 to 0.002). Stress had a significant negative impact on skin symptoms but not arm strength. Beneficial effects of meditation had half-lives of 48-59 days for skin symptoms and no detectable decay for arm strength. Benefits of visual imagery were more transient (half-lives 4-18 days). The effects of stress had half-lives of only 1-3 days.


COMMENT: These data demonstrated a significant relationship between meditation practice/imagery and recovery from dermatomyositis, possibly mediated by influences on the humoral immune system. The decay rate of meditation and visual imagery was much slower than that of stress. Since dermatomyositis is a humorally mediated immune microvasculopathy, these meditation and imagery benefits support growing evidence showing that these techniques influence immune function. A single case report can point the way to the need for large controlled studies, but the concern for side effects attendant to the use of pharmaceuticals is absent here. The greatest risk with meditation and visual imagery is that it might not work.

Stress and the Immune System

This meta-analysis of >300 studies on stress from 1960 to 2001 encompassing 18,841 subjects describes 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 include acute stress in which the immune system battles infections and other physical traumas. Brief situational stressors (such as exams) tended to suppress cellular immunity while preserving humoral immunity. Long-term stress fell into 3 categories: challenges which have a limited scope and some end-point; long-term stresses which 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). Subjective reports of stress generally were not associated with immune changes. In some cases, physical vulnerability as a function of age or disease also increased vulnerability to immune change during stressors.


COMMENT: Meta-analyses, particularly of hundreds of studies, should carry more significance than individual studies, especially for broad conclusions. In this instance, differences in acute and chronic stress effects are apparent, and suppression of both humoral and cellular immunity were shown in the studies of chronic stress. None of this should be a surprise, but confirmation on such a large scale is always welcome. One could conclude here that the ubiquitous nature of the maladaptive effects of chronic stress deserve attention in all situations in which practitioners assess patients for stress, and in all situations where stress would classically tend to emerge.

Mental Arithmetic and the Immune System

The role of the autonomic nervous system in secretory immunoglobulin A (sIgA) responses to laboratory challenge was explored in a study in which sIgA and cardiovascular activity were recorded at rest and during mental arithmetic and paced breathing. These tasks were selected to preferentially engage the sympathetic and parasympathetic nervous systems, respectively. Mental arithmetic elicited a mixed pattern of increased α- and β-adrenergic activity and a reduction in parasympathetic activity; systolic and diastolic blood pressures and total peripheral resistance increased and the pre-ejection period and heart rate variability decreased. In contrast, paced breathing primarily elicited an increase in parasympathetic activity and heart rate variability increased. Mental arithmetic also provoked an increase in sIgA concentration but no change in saliva volume, whereas paced breathing affected neither sIgA concentration nor saliva volume.


COMMENT: These data suggest that sIgA responses to laboratory stresses are mediated by sympathetic rather than parasympathetic processes. Of interest here is also the confirmation that requiring mental arithmetic as a standard form of laboratory-induced stress is probably valid. And we ask patients to do it (remember "count back from 1000 by 7s" as part of the mental examination?) when we evaluate them. Of interest as well is the notation that paced breathing elicited a significant parasympathetic response. Specialized breathing programs (e.g., the Butekyo program) have been found very effective in clinical relaxation training and in improving pulmonary function.

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@nwi.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.

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