Conference Perspective  
NEUROIMMUNOMODULATION: STRESS AND IMMUNE FUNCTION  
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At this meeting, as at a number of recent meetings wherein the latest cellular and  
molecular techniques have been used to revisit and re-evaluate long-standing  
biological questions and observations, the past has indeed become prologue. In many  
cases, as with sections of this meeting, the questions or observations are 25–30 years  
old, such as the seminal studies by Dr William R Beisel and his colleagues at the US  
Army Medical Research Institute of Infectious Diseases. This series of studies  
documented the relatively constant constellation of metabolic, physiological and  
endocrinological changes which occur during bacterial, viral and rickettsial diseases in  
humans and other species. The wisdom of the ancient Greeks also was demonstrated  
at this conference: the virtues of a sound mind in a sound body.  

The meeting began with Dr Seymour Reichlin (New England Medical Center and  
Vail, Arizona) listing both the clinical conditions and preclinical data that attest to the  
presence and consequences of neuroendocrine–cytokine interactions. As some of the  
consequences of such interactions he cited: pituitary–adrenal activation; inappropriate  
ADH secretion; sick euthyroid syndrome; sick hypogonadal syndrome; sick bone  
syndrome; impaired insulin secretion and insulin resistance; and sick brain syndrome,  
also known as sickness behaviour. In every case there is growing evidence of  
endocrine–cytokine interactions. Moreover, these interactions between cytokines and  
neurohormones may elicit adverse neurological side-effects when cytokines are given  
therapeutically. For example, in a 1987 study of 44 patients given IL-2 and  
lymphokine-activated killer cells, 5 patients developed moderate cognitive  
impairment, 22 displayed delirium and severe cognitive impairment, while 7 exhibited  
delusions, escape behaviour and picking at their bedclothes (the last a condition which  
Dr Reichlin noted was described by Galen and is often found in the severely ill).  
Interferon-α treatment of hepatitis C also is generally accompanied by fever, chills  
and fatigue, but in 17% of cases evokes serious brain dysfunction to include suicidal  
tendencies.  

Dr Rodney Langman (Salk Institute for Biological Studies) argued that the  
immune system ‘hijacked’ existing effector functions to create a scheme whereby the  
host can distinguish between self and non-self. He suggests that the immune system is  
unique to vertebrates while ‘immune responses’ can be found even in single-cell  
creatures. Dr Langman made an impassioned plea to begin collecting the data on  
cytokine and neuroendocrine effects and interactions in a central location so the
information can be processed and integrated into a ‘consensus model of neuroendocrine immunology’. He volunteered to be the contact person to begin collecting data on the ligands, the receptors and the cell types, as well as on the biological actions of, and physiological responses to, hormones and cytokines. Some in the audience thought that this would be an insurmountable task unlikely to yield much information about a complex system; however as meta-analysis has shown, computer systems can often find patterns in multiple sets of data that may not be apparent from individual studies.

Dr. Edward Bernton (Walter Reed Army Medical Center, Washington, DC) reminded the audience that despite the bloody nature of battle, it was infections not injuries that have caused more casualties in war, even as recently as the Korean, Vietnam and Gulf wars. In addition to being hazardous, war and the training for war is stressful. To assess the effects of such stresses on the endocrine-immune system(s) 300 Ranger trainees were studied over a period of 8 weeks during the desert, mountain, forest and swamp phases of their training. On average these healthy individuals lost 9–10% of their body weight, virtually all as fat, had 3–4 hours of sleep per day, operated at a high level of activity, and were subjected to a wide variety of stresses such as might occur in battle. By the end of the 4th week, at the completion of the mountain phase of training which was the most strenuous phase, serum cortisol levels increased while those of testosterone and IGF-1 decreased. At this time, the skin test to an array of antigens was 40% of normal while 20% of the trainees were anergic. The skin test response correlated with testosterone levels. While T cell function was decreased, IgE levels were increased. White cell secretion of IL-1α, IL-6 and TNFα in response to endotoxin was decreased. Attempts to eliminate these alterations in the neuroimmune responses by increasing food intake yielded equivocal results.

While exhausting exercise coupled with sleep deprivation and a variety of additional stresses clearly is immunosuppressive, according to Dr. Laurie Hoffman-Goetz (University of Waterloo, Ontario, Canada) acute maximal exercise by itself appears to increase the number of natural killer (NK) cells and increase NK and lymphokine activated killer (LAK) cell activities. Whether these increases in natural immune functions have benefit to the host may depend upon the nature of the disease, for example, the dissemination of mammary adenocarcinoma tumours appears to be unaffected by NK or LAK cell activity.

In regard to stress, it appears to make no difference whether one is man or mouse. Dr. John Sheridan (Ohio State University) showed that restraint stress increased plasma corticosterone levels and tissue responses to norepinephrine, but reduced the cellular immune responses of C57 Black 6 mice to respiratory influenza A infection. The elevated plasma corticosterone levels correlated with reduced lymphocyte trafficking to the lungs and to the draining lymph nodes of the infected mice. While cell accumulation at the inflammatory site and lymphadenopathy were restored by treating the animals with a glucocorticoid receptor antagonist, restoration of T cell activation only occurred when a β-adrenergic receptor antagonist was given, suggesting a role for catecholamine in the regulation of T cell activation.

According to Dr. Bruce McEwan (Rockefeller University), glucocorticoids can modulate immune cell trafficking as a function of the glucocorticoid receptors on such cells, as well as of tissue factors such as corticosteroid binding globulin and steroid catabolizing enzymes. Diurnal and stress-induced increases in glucocorticoid elicit