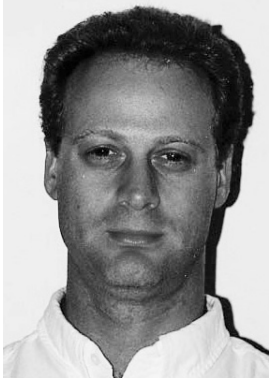
IMMUNE SYSTEM RESPONSE TO STRESSORS

Stress is ubiquitous and as such, some understanding of the dynamics of stress and its relation to health is necessary in the primary health setting.



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Stress is a dynamic process that describes a system under strain and the adaptive responses that are generated in order to maintain a balanced internal state. This strain is essentially a threat to the integrity of the organism and may be either physical (such as an infection) or psychological (such as bereavement); these are what are commonly understood as stressors. Once the organism has percieved the threat, a stress response is activated, primarily to generate energy to either fight or flee. Stressors and stress response together constitute stress. While the body is generating energy, it simultaneously down-regulates physiological systems that consume a lot of energy such as the gastrointestinal tract and certain components of immune function. This is mediated via a cascade of stress-related molecules released from the neuroendocrine system and the adrenals, which is rapidly activated and usually dissipates within minutes to hours, returning the system to its dynamic baseline once the threat has passed. This is adaptive and healthy; however, when the process is activated continuously or does not get deactivated, the result is a maladaptive one in which the overexposure to stress-related molecules (which in the short term are protective) becomes pathophsyiological.[1,2]

For example, if immunity is down-regulated in the short term and the stress response continues over time, the system is predisposed to more sustained immune suppression. This stress-related immune suppression is increasingly well understood and will be descibed here in some detail. While the clinical relevance of the research is clearer in certain patient populations – such as the elderly or those already immune compromised – the applicability to broad patient populations is more complex.

Two key concepts underlie the impact of stress on immune function. Firstly most chronic, maladaptive stress has a significant psychological component for the simple reason that we succumb rapidly to physical stressors while psychological and social strain can grind on for years. Modern brain imaging techniques offer insight into the relationships between neural networks and processes such as cognition, emotion and memory.[3] This initimate mind/brain relationship leads to the second important concept, namely that the brain and immune system are closely related via functional neuroendocrine-immune pathways.

The unique and individualised way that we each interpret what happens to and within us is one of the primary psychological processes determining whether a stimulus is perceived as threatening. The result of this is the activation of the stress axis. For example, one person may perceive public speaking as creative and exciting, while another may perceive it as stressful and, as such, will activate the hippocampal-hypothalamic-pituitary-adrenal axis while the former will not. The pathways between the brain and immune organs and cells are the physical link by which mind/brain phenomena – such as the perception that public speaking is stressful – can literally change the way in which the immune system functions. Moreover these same pathways allow for reciprocal communication so that the brain and the mind may be appropriately altered in response to immmune activation, as occurs during infectious illness.[1,2,4]

In the early 1980s researchers identified for the first time the presence of neuropeptides in cells of the immune system. Until that time the immune system was considered an essentially autonomous sytem, so the identification of the pituitary peptides endorphin and corticoptrophin (ACTH) resulted in a re-examination of the relationship between these 2 systems. Over 25 years of laboratory research has confirmed unequivocally that the cells of neuroendocrine and immune systems are linked not only structurally via the autonomic nerves, but essentially share a common molecular language.[5] That is, molecules of communication and their specific receptors in the brain (neuropeptides and neurotransmitters) are produced in cells of the immune system (from immune cell DNA) while immunopeptides and their recognition molecules are produced in certain discrete areas of the brain, particularly the systems involved with homeostasis, emotion and memory. These molecular pathways are functional (rather than simply theoretical), with this dialogue being the basis by which the effects of stress on immune function may be measured through access to immune cells in the peripheral blood.[4] For example, aspects of cellular immunity may be assessed by measuring the capacity of lymphocytes to divide or the ability of natural killer cells (NKC) to effectively kill micro-organsims or cancer cells. Humoral immune function may be measured by looking at the concentration of antibody to a specific antigen, such as the influenza vaccine (the higher the concentration, the more effective the immune response).[6]

Because of the idiosyncratic nature of perception, the effect of stressors on immune function in humans is best understood as an indirect measure of stress. Nonetheless, the evidence is unequivocal that psychosocial stress – be it the wear and tear of daily life, bereavement, divorce or writing examinations – results in suppression of various immune measures. For example, medical students showed significant reduction in humoral immunity and cytokine production during examinations compared with normal term time, while men with more recent stressful life events showed greater decline in NKC function during an arithmetic challenge than similar men with fewer life changes.

One of the best documented models of long-term, stress-induced immune dysregulation is that of men and women who provide long-term care for a family member with a serious medical condition such as Alzheimer's disease (AD). Lymphocyte proliferation, NKC and antibody response to influenza vaccination are all suppressed in this group, with the immunosupressive changes often persisting for years after the caregiving ends. Other chronic stressors associated with immune alteration include work burnout, unemployment, job strain and marital discord, all problems that are encountered daily in general practice.[7]

In the laboratory setting where animal models are used, the stress-associated immune changes are invariably related to overt disease. In humans, on the other hand, stress-associated immunosupression does not have an impact on health in a simple cause and effect fashion. Rather, genetic predispostion, age, pre-existing immune baseline, lifestyle choices (such as smoking, nutrition and exercise) all converge with stress-related effects on immunity to generate health changes.

As such, in a primary health setting, clinicians should be vigilant with certain patient populations who report being stressed – the elderly, diabetics, patients on immunosppressive agents, patients with HIV/AIDS, those with concurrent chronic conditions – who are at greater risk for immune-related illness. Because the chronic stress response has a systemic effect, susceptible patients are at risk for not only immune-related disorders (such as infections), but also stress-induced cardiovascular, gastrointestinal or dermatological illness, depending on genetic predisposition.[2,7,8]

Despite the caution in certain groups, anyone is potentially at risk of the effects of chronic stress. We might consider stress a risk factor for illness and as such, the primary health setting is an ideal place to begin basic aspects of stress management. It may be useful to integrate self care into primary care using stress reduction techniques such as relaxation therapy, meditation, yoga and biofeedback, which have been shown to have a positive impact on illness, as both a therapeutic and preventive measure.[9]

The public and media alike often talk of 'enhancing the immune system' because of the impact of stress. It would be more accurate, and in fact more useful, to suggest to patients that the goal is a balanced immune system (as opposed to a suppressed or enhanced one), and this is best achieved by a balanced individual[10] living a balanced lifestyle which includes exercise, good nutrition, emotional intelligence, social connectedness and time for quiet reflection.

References available on request.

IN A NUTSHELL

Acute stress is adaptive and protective.

Chronic stress is maladaptive and pathogenic.

Most chronic stress has a significant psychological and/or social component.

Perception of events, either internal or external, will determine whether the stress axis is activated.

The functional neuroendocrine-immune pathways, based on a shared molecular language, is the basis by which the mind/brain affects the immune system.

Most chronic stress is immunosuppressive.

Certain patient populations are at greater risk of stress-associated immune suppression causing immune-related illness.

Stress should be considered a risk factor for illness rather than a cause.

Stress reduction can be implemented at the primary health care level as a therapeutic and preventive tool through the integration of self care into primary care.

A balanced immune system is optimal for health and is founded on a balanced lifestyle.