

Psychoneuroimmunology and the Nature of Disease

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Disease is often described as man's mortal enemy. This is largely supported by the scientific model of pathophysiology which developed out of the Renaissance, wherein observation replaced memorization of established medical models as the key tool for understanding disease. With the development of the basic sciences and notably the discovery of pathogens, a model of the body as a compartmentalized organic machine which could fall prey to defect evolved. Indeed, the great focus in biomedical research of the Twentieth Century has been concerned with infectious disease, a field understandably permeated with an "us versus them" mentality.ⁱ However, an increasing pool of scientific data in the emerging field of psychoneuroimmunology is challenging this compartmentalized model of the human body which villifies disease, suggesting, rather, that disease symptomatology is more of a messenger imparting valuable information through a highly integrated system for the individual, if not for the species, to use for its survival.

Psychoneuroimmunology is the study of the interaction between behavior, the nervous system and immunity. Although intuitive knowledge of the connection between lifestyle and disease susceptibility predates history, scientific validation was scant prior to the development of quantifiable measures of immunity. However, recent advances in the utilization of cellular and protein markers have enabled researchers to better study interactions between the neuroendocrine, neurochemical and immune systems. In addition, whereas infection had been the leading cause of disease in centuries past, the chronic stress-related diseases account more and more for today's morbidity and mortality.ⁱⁱ It is, therefore, fitting to begin this discussion of the "mind-body-immunity connection" with the increasingly familiar topic of stress.

Stress can be defined as an altered neuroendocrine state resulting from perceived threats to mental or physical well-being.ⁱⁱⁱ The principal identified pathways which are activated with the stress response are the sympathetic adrenal medullary system, mediated through the release of catecholamines through the bloodstream, and the hypothalamic pituitary adrenocortical system, largely mediated through the release of cortisol.^{iv} While these neuroendocrine pathways evoke the fight-or-flight and conservation-withdrawal responses so beneficial for evolutionary survival, chronic activation of these autonomic systems has been correlated with increased morbidity.^v

It has been repeatedly demonstrated that psychosocial factors such as personality styles, coping skills, interpersonal relationships and emotional experience influence autonomic tone,^{vi} and that techniques such as stress management and relaxation are consistent with a decreased responsivity to plasma norepinephrine and decreased baseline cortisol levels.^{vii} Hypertension and coronary artery disease treatment programs have demonstrated increased efficacy when stress management skills are introduced.^{viii, ix} Finally, a wide range of animal studies suggests that the presence of quality social relationships can inhibit posterior hypothalamic zone activity and hence secretion of cortisol and catecholamines. These data correlate well with human studies which suggest that the quality of one's social relationships, or lack thereof, rivals cigarette smoking, obesity and physical activity as a major risk factor for health.^x In fact, social integration has been shown to significantly lower mortality among persons with Type A personality, long correlated as a risk factor in the development of stress-related disease.^{xi} These findings support a "mind-body connection" model wherein behavior influences physiology.

There is now an increasing body of evidence to support a new addition to the "mind-body" model, namely the immune system. Long maintained as an autonomous host defense system, the immune response is increasingly being viewed as highly integrated with the stress response. Cortisol is an immunosuppressive hormone, and since it is released as part of the inflammatory response, it is believed to serve as a negative feedback signal to hold the immune system in check. While the autonomic nervous

system innervates visceral organs like the heart and stomach, it has also been demonstrated to sympathetically innervate immune organs such as the spleen, thymus, bone marrow and lymph nodes.^{xii} Immune organs and cells have been shown to contain receptors for most hormones and neurotransmitters,^{xiii} and to actually contact sympathetic nerve terminals with the ultrastructural features of synaptic contacts. The course of immunity has been shown to change when lymphocytic hormone receptors are blocked. Furthermore, a variety of immune processes can be altered through electrical stimulation or lesions of the hypothalamus, known to play a key role in regulating autonomic processes.^{xiv} Such evidence suggests that the brain provides important regulatory control over the immune system.

A wide variety of stressors have been shown to suppress some aspect of immunity, including: social defeat, electric shock exposure, loud noise, immersion in cold water, restraint, crowding and maternal separation.^{xv} Psychological stress has been shown to increase the risk of acute respiratory illness in a dose-response manner to a wide cross section of viruses, suggesting that stress suppresses a host's general resistance and thereby increases one's susceptibility to multiple infectious agents.^{xvi} A number of immunologic changes have been observed in students undergoing examination stress, including reductions in: B- and T- lymphocyte counts, lymphocytic interferon production, and natural killer cell activity.^{xvii}

The effects of chronic stress also appear to be immunosuppressive. Studies comparing immune parameters among residents living in the stressful environment surrounding the Three Mile Island nuclear power plant demonstrate fewer B- cells, suppressor and cytotoxic T-cells and natural killer cells, which were negatively related to catecholamine levels, when compared to control groups living in other areas. Prolonged unemployment has been correlated with a reduced lymphocyte response to various antigens. Decreased T-cell and helper:suppressor T-cell ratios have been demonstrated in those caring for relatives afflicted with Alzheimer's disease.^{xviii}

The immunosuppressive effect of social disruption and depression has also been studied. As already noted, social support constitutes a major health risk factor, and this is especially visible when considering bereavement and divorce. One group of bereaved men demonstrated a reduced lymphocytic response to antigens relative to prebereavement levels. Significant reduction in Natural Killer cell activity has also been observed in recently bereaved women. Increases in self-reported illness and in antibody titers to Epstein-Barr Virus and Herpes Simplex Virus-1 have been observed in divorced or separated subjects, suggesting decreased immunocompetence at fighting viruses. It should also be kept in mind that affect appears to influence immunocompetence. Secretion of salivary IgA has been shown to be significantly less when a negative mood was reported than when a positive mood was reported. Lower absolute numbers of B- and T- cells, decreased lymphocytic response and increased plasma cortisol levels have been demonstrated in patients hospitalized with major depressive disorder. Finally, reduced Natural Killer cell activity has been correlated with out-of-normal scores on ten of the twelve subscales measured in the Minnesota Multiphasic Personality Inventory, suggesting that better mental health in general is associated with increased Natural Killer activity.^{xix}

While environmental stressors appear to have an immunosuppressive effect, research also indicates that an individual's personality and style of coping with stress affects immunity. It has been shown that people who display a higher need to have power and influence over their environment than their need to affiliate with others demonstrate lower salivary IgA concentrations and higher frequency of reported illness than others. Similarly, people who display a high level of self-restraint or activity inhibition have been shown to have lower IgA secretion during times of stress and less ability to recover after period of stress than those who exhibit stronger affiliative motives.^{xx} Interestingly, high denial ability to repressively cope with perceived threats has been associated with lower plasma cortisol levels than those with persisting thoughts of perceived threats,^{xxi} which suggests that certain coping styles may enable individuals to diffuse the perceived threat of psychosocial stressors, before immunosuppression occurs.

Given the ample evidence that psychosocial phenomena affects the immune system, it follows that behavioral interventions could be employed to beneficially regulate immunologic functioning. Classic Pavlovian Conditioning studies, wherein a taste paired with immunomodulatory drugs yield learned modulation of immunity when taste is reintroduced without the drugs, have demonstrated that both suppression and enhancement of the immune response can be produced with appropriate conditioning. It has been demonstrated that the beneficial immunosuppressive effects of the toxic drug cyclophosphamide, used to treat the autoimmune disease Systemic Lupus Erythematosus, can continue after cessation of the drug when it is paired with a neutral stimulus which is not discontinued.^{xxii} Such conditioned immunosuppression may also prove beneficial in the field of organ transplants by facilitating a delay in

tissue rejection without the use of toxic drugs. It has been observed that women who had undergone chemotherapy in the past, displayed non-medically mediated immunosuppression when merely brought back to the same hospital. Evidence of such conditioned immunosuppression argues for innovative therapeutic contexts in which chemotherapy could be performed to extinguish learned immunosuppression.^{xxiii}

In addition to classical conditioning modalities, the immunomodulatory potential that psychotherapeutic modalities could offer is far-reaching. Relaxation training alone has been shown to significantly enhance Natural Killer cell lysis activity and reduce Herpes Simplex Virus antibody titers.^{xxiv} Based on the above cited evidence, stress management skills could greatly reduce the morbidity associated with major life changes and chronically stressful life circumstances, if not provide immunoenhancing effects in the face of everyday hassles and stressors. Psychotherapy may prove beneficial to mental health as well to physical health by not only enabling persons to work through diseases like depression, but also by modifying behavior, personality styles and coping systems to enhance immunocompetence.

While the implications of a mind-body-immune circuit are far-reaching, an increasing body of evidence suggesting that this circuit is bidirectional may be equally significant. If the brain is to be considered as playing a key regulatory role in the immune response, it follows that it would receive information along some well defined pathway, since the immune response occurs outside the central nervous system. Indeed, the immune response does change both chemical and electrical activity in the brain. Hypothalamic neural activity has been shown to increase as the B-cell proliferation peaks in response to a harmless antigen. Cytokines, once thought to be messengers merely between cells in the immune system, have now been shown to produce alteration in brain electrical activity. Receptors for the cytokine interleukin-1 have been demonstrated in the central nervous system, and it could be that cytokines are the means by which the immune system communicates with the brain, perhaps via peripheral autonomic nerve pathways.^{xxv} Recognizing such communication, the immune system may be appropriately viewed as a sensory organ which conveys vital information to the brain.

Increases in autonomic tone have been shown to accompany the immune response, which suggests a physiological pathway common to both the stress and inflammatory responses. Indeed, cortisol is secreted in both responses. However, whereas cortisol is released immediately in the stress response, quickly enhancing cardiac output, vigilance and analgesia and otherwise shunting energy to the brain and muscles to facilitate survival in a fight-or-flight situation, the release of cortisol is delayed in the inflammatory response. This delay may be accounted for in the complex sequence of events, largely mediated by the cytokines, involved in mounting the inflammatory response. Cytokines directly stimulate the hypothalamus, and can thereby initiate a full hypothalamic pituitary adrenal response. Interestingly, administration of IL-1 to animal models can produce all of the well-characterized behavioral changes found in animals exposed to fear or anxiety-arousing stimuli. These changes in behavior include decreased food and water intake and activity, reductions in social interaction and willingness to engage in sexual behavior, and decreased tendencies to explore novel objects.^{xxvi} Such findings suggest that the immune system not only communicates with the brain, but that it also influences behavior.

The recognition that psychophysiology influences immunity and that the immune system, in its own right, influences psychophysiology challenges the well-established notion that the body is a compartmentalized machine wherein the nervous systems and immune systems perform their functions in a autonomous fashion. In fact, it challenges the notion that the brain is, in a hierarchical sense, the center of command. The immune system likely predates the central nervous system in evolutionary terms,^{xxvii} and since the development of both systems clearly offers benefits to survival, it stands to reason that they would be highly integrated with one another.

Psychoneuroimmunologic findings suggest that illness can be viewed as a warning signal, communicated through the body, that change is needed. The more researchers learn about how behavior modification can enhance health, the more logical it seems to use the message which illness imparts to examine how the entire mind-body system is functioning as a whole.^{xxviii} From this perspective, even death may be viewed, not as a failure, but as information valuable to the survival of the species. There is indeed a strong message carried to the health professions in the increasing number of patients presenting with stress-related diseases to the health care community. Though society is understandably slow to break free from well established medical models, one only needs to observe the current trends in illness to realize that a change in the present approach to health care is called for.

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