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Selections from Current Literature
Psychoneuroimmunology: validation of the biopsychosocial model

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Introduction

The biomedical model has been extraordinarily successful as evidenced by the dramatic technological advances of the 20th century. Medical investigators identified bacteria and viruses as the cause of many diseases, thereby, replacing the attribution models of 'miasmas' and supernatural forces held by prior generations. While we have witnessed an era marked by exceptional medical advances through scientific reductionism, these have come at the expense of fragmentation and depersonalization of patient care. In this era of mechanistic thinking, George Engel raised concern that the body is viewed as little more than a machine, disease as the breakdown of the machine, and the physician's sole job is to fix the machine once broken.[1] Psychosocial variables and their effects on health, i.e. the importance of looking at an illness within the context of the person and their life stresses and habits, if considered at all were deemed to be outside the domain of medicine. These factors are not easily studied using a reductionism model. Within the medical community, it became apparent to a few that lack of consideration of the context of illness, the medicalization of life problems without addressing the patient's life story, and fragmentation of medical care did not fully meet patients' needs. These glaring health care deficiencies led to the development of the discipline of Family Medicine[2] that adopted as one of its basic tenets the Biopsychosocial Model.[1]

While many clinicians intuitively gave equal credence to biomedical, psychological and sociological parameters when managing clinical problems, hard evidence necessary to effect a paradigm shift within medical schools, medical practice and society in general was lacking. Clinical experiences convince us, through inductive reasoning, that external stresses exacerbate and may even cause illness. But where are we on the time-line, within the framework of science, in answering these clinical questions:

- How does everyday stress affect the immune response?
- What are the health consequences of stress-related immunological changes?
- Does chronic stress promote persistent immunological dysregulation?
- Can management of stress and alteration of its immunological and endocrine effects alter or cure disease?
- Has there been valid research that can help address these clinical questions?

It is the purpose of this paper, and subsequent others in this series, to introduce some interdisciplinary, collaborative research that has given rise to the field of psychoneuroimmunology. These are studies that help validate the importance of the contextual approach to medicine.

Kiecolt-Glaser JK. Stress, personal relationships, and immune function: health implications. *Brain, Behavior, and Immunity* 1999; 13: 61–72.

This excellent review initially was presented as the Norman Cousins Memorial Lecture to the Psychoneuroimmunology Research Society. It cites several collaborative studies between this clinical psychologist and an immunology laboratory that address the question of whether commonplace stressors such as students' examinations could down-regulate immune function. In addition, the author cites earlier studies by others that dealt with different stressors, i.e. bereavement, astronauts' responses to space flight, noise and sleep deprivation. She then cites subsequent intervention studies to assess whether stress-reducing interventions have positive effects on immune function. Lastly, she considers studies correlating effects of personal relationships to immune function.

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The author's early work in the 1980s consisted of a series of prospective studies of medical students' responses to examinations. These data showed transient changes in multiple facets of the cellular immune response and its mediators, including decreased natural killer (NK) cell activity, decreased γ-interferon (IFN-γ) production by lymphocytes stimulated with concanavalin A, increased plasma and intracellular levels of cyclic AMP, and decreased proliferative responses to mitogens prior to important examinations.

In one study, students' immune response to a series of three hepatitis B inoculations given on the last day of a 3 day examination series were measured. A quarter of the students seroconverted after the first inoculation. These students were less stressed. Measured by validated instruments, these students were less stressed than those who did not seroconvert until after the second inoculation.

Subsequent studies discussed in the article evaluated whether interventions that reduced stress could have positive effects on immune function. In one such study, 45 adults were assigned randomly to one of three protocols: (i) relaxation training; (ii) social contact; or (iii) no intervention. Relaxation subjects had a significant enhancement of NK cell activity at the end of the 1-month intervention, as compared with the other two groups which were unchanged. This was the first evidence, from a well-controlled study, of immune enhancement from a behavioural intervention.

Another of the author's studies investigated use of a hypnotic/relaxation intervention as prophylaxis for some aspects of cellular immunity if used before a stressor was introduced. Again, medical students were assigned randomly to control and experimental hypnotic/relaxation groups that met in the interval between baseline and examination. While NK cell activity and percentages of helper T-lymphocytes declined in both groups during examinations, subjects in the hypnotic/relaxation group showed variability. The more frequently hypnosis was practised, the higher the helper T-lymphocyte percentages during exams.

Comment

It is intriguing that seminal research in immunology and the central nervous system from the late 1970s and early 1980s has not found its way into medical halls of academia. (Such has been the case with data demonstrating physical links for neural modulation of immunity.) This suggestion of communication between the CNS and immune cells comes from discovery of B-adrenoreceptors in T- and B-lymphocytes[3,4] as well as the existence of other neuroreceptors, i.e. endorphins[5] on the surface of immune cells. One cannot help but ask the question, "If the brain is capable of exerting some influence on the modulation of immune responses, can the CNS convey the effects of psychosocial factors on a variety of immunologically mediated pathophysiological processes."[6]

As the author herself points out, evidence that the immune response to a vaccine can be modulated by examination stress in young, healthy adults (who are already medical students and adept at test-taking) is a finding with public health implications. Additionally, these data might be extrapolated to raise the hypothesis that the body's response to other pathogens such as viruses or bacteria may be compromised under stress. Students who were more stressed and anxious in this study seroconverted later, suggesting that these same students might also be slower to develop an antibody response to other pathogens. Indeed, the author points out that the incidence of self-reported infectious illness symptoms increased around examination periods.[7]

Castes M, Hagel I, Palenque M, Canelones P, Corao A, Lynch NR. Immunological changes associated with clinical improvement of asthmatic children subjected to psychosocial intervention. *Brain, Behavior, and Immunity* 1999; 13: 1–13.

This prospective study evaluated the impact of a psychosocial intervention (PSI) on immunological parameters and the clinical status of a group of asthmatic children of an island population in Venezuela. Thirty-five asthmatic children were assigned randomly to either a PSI or a control group. Both groups received conventional asthmatic treatment. The PSI consisted of a 6-month programme including relaxation, guided imagery and self-esteem workshops. The authors report that during the PSI, the number of asthmatic episodes and use of bronchodilator medication were significantly reduced, and pulmonary function improved significantly compared with 6 months prior to intervention. There was also a significant reduction in the specific IgE responses against the most important allergen in these subjects, *Ascaris lumbricoides*. PSI resulted in a significant increase of NK cells, an augmented expression of the T-cell receptor for inerleukin-2 (IL-2) and a significant decrease of leukocytes with low affinity receptors for IgE. These surface markers became similar to those of non-asthmatic children. These clinical and immunological changes were not seen in the control group.

Comment

It is known that an important component of asthma is the stimulation of IgE responses by environmental allergens; sensitization of mast cells by this antibody and subsequent degranulation of these cells[8] releases vasoactive and brochoconstrictive amines and leukotrienes which attract inflammatory cells such as eosinophils and macrophages. CD4 and helper T-cells exhibit a Th2 phenotype.[8] These cells induce IgE synthesis via the production of IL-4. Allergen-specific Th2 cells are selectively enriched in tissues affected by allergic inflammation such as the bronchial mucosa of asthmatics. The literature acknowledges the importance of psychological influences in asthma. The importance of this study,

however, lies in its ability to demonstrate that a PSI was not only able to lead to clinical improvement in these asthmatic children, but also led to a simultaneous improvement in immune processes associated with asthmatic pathophysiology. The authors point out that of particular relevance are the immunological changes reflected by the leukocyte surface markers. At the beginning of the study, they noted a significantly lower level of NK cells in the asthmatic children than in non-asthmatic children from the same population. This could be related to a low expression of the IL-2 receptor as it has been reported that IL-2 stimulates the production of NK cells.[10] The PSI resulted in a significant increase of NK cells that was accompanied by an augmented expression of the T-cell receptor for IL-2. Because NK cells are an important source of IFN-γ,[10] and this cytokine inhibits IgE synthesis, the augmented level of NK cells after PSI may have contributed to the reduced specific IgE levels observed.

Smyth MM, Stone AA, Hurewitz A, Kaell A. Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis, a randomized trial. *Journal of the American Medical Association* 1999; 281: 1304–1309.

In this randomized controlled trial, the authors test the hypothesis that writing about stressful life experiences affects disease status of patients with asthma or rheumatoid arthritis evaluated by standardized quantitative outcome measures. The sample size consisted of 112 patients (61 asthma, 51 rheumatoid arthritis). Patients were assigned to write about either the most stressful event of their lives (experimental arm) or about emotionally neutral topics (controls). Asthmatic patients were evaluated with spirometry, and a rheumatologist clinically examined rheumatoid arthritis patients. The rheumatologist utilized a structured interview designed to rate diagnostic symptoms, a global assessment of disease activity, symptom severity, distribution of pain and swelling, presence and severity of deformities, assessment of daily living capacity and psychosocial functioning. There were baseline, 2-week, 2-month and 4-month assessments performed after the writing assignment. The assessors were blinded to the group assignment of the subjects. Asthmatics in the experimental arm had improvements in lung function; controls showed no change. Rheumatoid arthritis patients in the experimental arm improved in overall disease activity; controls did not change.

Comment

The author, James Pennebaker, PhD, has been investigating the effects of an apparently simple and benign intervention since the mid-1980s. This intervention consists of getting individuals to write for 15–30 minutes on 3–5 consecutive days about a traumatic or otherwise emotional experience that, in many cases, they had not disclosed to anyone else. He has described improvements in health in terms of fewer office visits and self-reported symptoms. Several studies demonstrated increased immunocompetence. College students improved their grades and, in one study, a group of unemployed engineers were more likely to find new jobs than out-of-work controls.[11]

The implications of these studies and that of Smyth are that the process of disclosure may be beneficial psychologically and physiologically. This study adds to the literature suggesting that addressing patients' psychological needs produces health benefits and firmly supports a biopsychosocial approach to medicine.

Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. *Lancet* 1995; 346: 1194–1196.

In this prospective study, the authors investigate the effects of stress, caused by caring for a relative with Alzheimer's disease, on wound healing. Thirteen women caring for relatives suffering from dementia were matched for age with 13 controls. Both groups underwent a 3.5 mm punch biopsy wound. Wound healing took significantly longer in caregivers than in controls. Peripheral blood leukocytes from caregivers produced significantly less IL-1β mRNA in response to lipopolysaccharide stimulation than did controls' cells.

Comment

Proinflammatory cytokines such as IL-1, IL-8 and tumour necrosis factor (TNF) are involved in the protection against infection, preparation for repair of injured tissue and enhancement of phagocyte recruitment and activation.[13] Additionally, cytokines released by these recruited cells are known to regulate the ability of fibroblasts and epithelial cells to remodel damaged tissue.[13,14] Moreover, dysregulation of cytokines can impair wound healing.[15] Thus, this study nicely correlates a clinical finding and its underlying pathophysiological, immunological change with an external, psychosocial stressor.

Conclusion

These articles that link clinical manifestations, the CNS and the immune system (internal events) with psychosocial stimuli (external events) validate the need for giving equal credence to biomedical, psychological and social parameters when managing patient illness. We are rapidly reaching a point where there is 'hard' evidence for these 'soft' issues. It is noteworthy that diseases and trauma cases previously considered so separate and distinct can have immunopathophysiology so similar. This is additional proof that the boundaries of medical systems, ergo specialties, established in medicine are truly artificial. These studies question the notion of an autonomous immune system. As more intervention studies

demonstrate an ability to modulate immune function through non-toxic, benign modalities related to adverse psychological stress, perhaps our approach to disease and illness will shift to one in which context plays a dominant role.

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