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Psychoneuroimmunology: introductory comments on its physics and metaphysics

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Psychoneuroimmunology (PNI), as an emerging field of science and medicine, has been challenged, first, by the extraordinary complexity of each of its interacting elements: the central nervous system, behavior, and the immune system. These interactions, in turn, must ultimately be tested empirically in relation to their consequences for physical health and disease. A second, and equally formidable challenge, has extrascientific origins. Psychoneuroimmunologic concepts can be extraordinarily attractive to patients and practitioners struggling to maintain personal autonomy in the face of medical technology and its attendant dehumanization. In their enthusiasm, many have gone well beyond the empirically delineated science of PNI. In the United States, there has been a sense of urgency among the lay public (and among some clinicians) to adopt observations from what is still primarily a patchwork of loosely linked observations to support novel but fundamentally unsubstantiated treatments for disorders such as cancer. Clinical enthusiasm for procedures such as guided imagery, linked initially to the even more primitive base of psychoimmunologic knowledge of 15–20 years ago, engendered a furious scientific backlash. Traditional immunologists and other scientists and physicians were confronted with a discipline that seemed to be promulgated by practitioners of (yet to be legitimized) alternative medicine and, possibly, outright charlatans. In 1984, the journal *Nature* published an editorial entitled 'Psychoimmunology: Before Its Time' (Maddox, 1984). The following year, the *New England Journal of Medicine* published an article that found no correlation between psychosocial factors and survival in patients with advanced malignant disease, accompanied by an editorial arguing that the influence of the brain and psychological states on immunity and health were likely to be of negligible clinical significance (Angell, 1985). These responses were, at least in part, an attempt to protect patients and families from treatments that were unsubstantiated, expensive and, in some cases, advocated as alternatives to established medical treatments with demonstrated (albeit limited) efficacy. The confrontation that emerged seemed at times to cross the boundary of scientific discourse and dissent, becoming a struggle for the souls of believers and skeptics. Some advocates of science began to lump the science of psychoimmunology with the healers who too enthusiastically embraced and expanded upon its findings.

The belief that emotional states (by today's science, 'the brain') can influence the immune system and health runs deep within Western culture and medicine (not to mention that of the East). Galen reportedly asserted that melancholic

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states contribute to the pathophysiology of breast cancer and many can quote family and other folk wisdom to attest that stress plays a major causal role in the development of infectious diseases and a host of other ills. The triumph of the germ theory, with its orientation to demonstrating singular causes for specific diseases, and the demonstration that the immune system can function independently of the brain, discouraged consideration of the immune system as having a multifaceted regulation, subject to multiple internal and external influences. Furthermore, on a methodologic level, many immunologists were, until recently, unprepared to countenance experimental paradigms designed to demonstrate only modest quantitative changes in laboratory measures developed initially as semiquantitative markers for the presence of an immunologic response. There was little evidence that a quantitative change in a measure such as mitogen response or natural killer cell activity could predict deterioration of immunologic function or clinical disease.

While arguments among lay advocates and scientific critics of the field proceeded, a number of reliable observations emerged in the 1960s and 1970s linking psychological states and the immune system. In the United States, this early work was associated primarily with the laboratories of George Solomon, Robert Ader, and Marvin Stein. Seminal studies by Solomon and coworkers in animals and humans demonstrated links between behavioral states, immune markers, and autoimmune and infectious disease (Solomon, 1993). Several groups (see Keller et al., 1991) demonstrated that stressors such as uncontrollable shock in rats and mice could result in suppression of lymphocyte activity as well as increased susceptibility to tumors. Furthermore, the effects could not be accounted for solely by the classic hypercortisolism of stress (e.g., Keller et al., 1983). Other studies demonstrated a host of neuroendocrine, neurotransmitter, and neuropeptide influences on the immune system as well as direct neural connections to immunoactive cells (see Solomon, 1993). Effects of brain lesions on immune activity were demonstrated as well as feedback loops from the immune system to relevant brain centers. Findings in animals showed that higher cortical functions could, in fact, influence the immune system. In an important series of studies, Ader and co-workers showed that a variety of immune responses were subject to behavioral conditioning (Ader and Cohen, 1991). Others found that the ability to control a stressor could mitigate both its suppression of the immune system and its enhancement of tumor growth in rodents (see Keller et al., 1991).

While methodologic complexity has limited the capacity to investigate immunologic change and clinical outcomes concurrently, several lines of research have hinted strongly at such clinical relevance. By the early 1980s, controlled studies in humans had demonstrated associations between major stressful events such as bereavement, themselves associated with increased morbidity and mortality, and altered immunity (e.g. Schleifer et al., 1983). Further studies provided evidence that stressors associated with psychoimmunologic changes in man can influence a variety of medical disorders (Kiecolt-Glaser and Glaser, 1995). A complicated relationship between depressive disorders and altered immunity has also been documented (Schleifer et al., 1989; Stein et al., 1991). More recently, new approaches to linking psychoimmunology with psychosomatic medicine, and specifically clinical outcomes, have emerged. Provocative studies demonstrated that clinical intervention such as supportive group psychotherapy may lead to decreased mortality in patients with both breast cancer and malignant melanoma (Spiegel et al., 1989; Fawzy et al., 1993). Such studies have even caught the attention of the corporate managers who play an increasing role in the allocation of medical services in the United States (Melek, 1996).

In contrast to its earlier struggle for even basic recognition, the late 1980s and early 1990s saw an unprecedented growth and interest in psychoimmunology. The field appeared to have found its time and its place. As the slowly accumulating data base of psychoneuroimmunology was beginning to pique the interest of traditional immunologists, that interest expanded exponentially, along with research funding, with the emergence of AIDS as an overwhelming clinical pheno-

menon in the United States. The extraordinary variability in the natural history of HIV, and the apparently crucial contribution of host factors in determining its course, raised expectations that psychoneuroimmunologic factors would be found to play a key role in the onset and progression of the disease. Furthermore, PNI methodologic strategies earned respectability as some of the same quantitative changes that had earlier been debunked as immunologically meaningless (e.g. in lymphocyte markers and in functional mitogen responses) now proved to be useful markers for the progression of HIV disease.

During this time, substantial funding was made available through the National Institutes of Health in the United States to support psychoneuroimmunologic research as a basic science relevant to the understanding and control of AIDS. Unfortunately, the extraordinary expansion of psychoimmunologic research and the heightened enthusiasm for the field may have again triggered unrealistic expectations. Disappointment ensued, at least initially, when the anticipated large effect of psychological states on the primary immunologic marker in HIV, circulating $CD4^+$ cells, was not readily demonstrable. Partly as a result, US policy again shifted, with substantial restrictions on the extent to which dedicated funding for AIDS research could be applied to basic psychoimmunologic studies. Only those projects linked directly to HIV disease itself remained eligible, and with more limited available funds. It is of note, however, that research on the psychoneuroimmunology of HIV, now utilizing more extensive longitudinal behavioral and immunologic assessments, has begun to delineate a role for psychological factors in the immunologic and clinical course of the disease (Goodkin et al., 1994; Leserman et al., 1997).

Psychoimmunology, as a field, may be said to have entered into a maturation phase. The belief that large and global changes in the immune system are a regular consequence of psychological events has given way to the recognition, predicted by some all along, that the immune system is a highly complex and internally counterbalanced system that does not respond wildly when exposed to environmental or internal stimuli. As an ancient, conserved biological system designed to maintain homeostasis in the face of external and internal antigenic challenge, one would anticipate that the immune system has developed as fundamentally adaptive and conservative of its function. Immune effects of biologically non-catastrophic stressors are therefore likely to be subtle, and may only be detected if a wide range of immune system parameters are assessed at relevant time intervals. Recent studies have recognized that developmental and psychobiological factors such as age and gender, genetic susceptibility and prior stress exposure, and the baseline biological status of the subject (and his or her immune system) will influence individual responses to psychosocial challenge. In humans, these often can only be inferred since investigators and clinicians are restricted to assessing tissues such as peripheral blood that usually provide only indirect evidence of underlying immunologic perturbation. Emerging methodologies for assessing more specific aspects of immune activity and mechanisms, such as secretion of and sensitivity to cytokines and examination of susceptible lymphocyte cellular mechanisms, may provide more reliable markers for immune system change. This is not to say that psychoneuroimmunology must be relegated to the fringes of clinical medicine. Discovery of patterns of susceptibility, of specific risk factors, may very well demonstrate substantial immunologic effects that have clinically important consequences in subgroups at risk for identified medical disorders. Focused interventions, whether psychological or biological, could then be devised for such individuals. The promise of conferences such as this is that the sharing of accumulating data will lead to identification of the specific psychological, neural, and immunologic parameters that interactively contribute to psychoneuroimmunologic outcomes.

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