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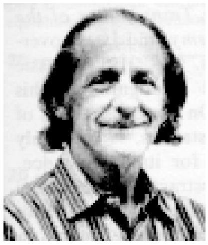

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Psychoneuroimmunology: A New Facet of the Mind-Body Dialogue

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Since ancient times, physicians have questioned whether the mind can affect health. Many anecdotal reports have claimed that patients overcame life-threatening illnesses by their will to live. But we lacked hard evidence that would explain the relationships between attitudes and disease. Recently scientists have uncovered new data that demonstrate a bidirectional link between the immune and the nervous systems. We are now beginning to understand how these two systems can interact to either set the stage for disease or enhance the prospects for a healthy body. Various names have been applied to this field, including psychoimmunology and neuroimmunomodulation. In this essay, I will use the term psychoneuroimmunology. This term was coined by Robert Ader, Department of Psychiatry, University of Rochester Medical Center, New York, to describe the emerging field that studies an organism's response to experience and the bodily system that operates to defend an organism against disease.[1]

Some of the earliest research on the mind-body connection involved studies of stress. In 1914 physiologist Walter B. Cannon, Harvard Medical School, defined what he later termed the fight-or-flight response. When the brain perceives stress, it signals the sympathetic branch of the autonomic nervous system, which regulates the "automatic" functions of the body, such as the heartbeat and the digestive processes. This results in an increased heart rate, faster breathing, and a rush of blood away from the skin, hands, and feet toward the deep muscle tissue. This action causes an increased supply of oxygen to flow to the muscles for use in either fighting or escaping the stressful situation.[2]

As early as 1936, Hans Selye, director, Institute of Experimental Medicine and Surgery, Montreal, observed three morphological changes that occurred in response to noxious stimulations. These changes included adrenal cortical enlargement, bleeding ulcers of the stomach and duodenal lining, and atrophy of the thymus and other lymphatic structures, a change that directly damages the immune system.[3] Selye was a pioneer in stress research. He wrote about his 1946 paper "The general adaptation syndrome and the diseases of adaptation" in a *Citation Classics®* commentary in 1977.[4] In this classic paper, he defined the general adaptation syndrome as the sum of all nonspecific, systemic reactions of the body that occur upon continued exposure to stress. Selye proposed that the adaptation syndrome may be directly related to disease. I used the 1946 paper in my first experiments on citation indexing.[5] Many years later I met this remarkable man who was one of the pioneers in medical information science.

In 1964 George F. Solomon, now of the Department of Psychiatry, University of California, Los Angeles, and Rudolph H. Moos, Department of Psychiatry, Stanford University School of Medicine, Palo Alto, California, published the first paper exploring the relationships of stress, emotion, immunological deficiencies, and physical and mental disease. Solomon and Moos used the term "psychoimmunology" to describe their early work on the effects of personality, stress, and emotions on immune-associated diseases. These include both immunologically resisted diseases (such as infections and cancerous diseases) and immunologically mediated diseases (such as allergies and autoimmune diseases).[6]

The development of concepts in psychoneuroimmunology began with clinical observations on the relationship of emotions and disease and progressed to clinical and experimental research on emotional factors and immunologically related disease. These theoretical concepts are only now beginning to be based on hard scientific data from well-controlled experiments on specific factors mediating resistance to disease. Contrary to public opinion, science is not made overnight. Moreover, the most accepted theories must be subjected to continual reevaluation.

More recently, the Institute for the Advancement of Health, New York, has been established to further the understanding of how mind and body interactions affect health and disease. The institute promotes research and acts as an information clearinghouse. Norman Cousins, professor of medical humanities, University of California, Los Angeles, School of Medicine, is a member of its Scientific Advisory Board. He startled the medical world by claiming that he cured himself of ankylosing spondylitis—a crippling disease that causes disintegration of the connective tissue in the spine. Cousins claims that his determination to keep a positive attitude toward regaining health played a major role in his recovery. While he is convinced that the mental state affects illness, Cousins realizes that the psychological powers of healing will never be fully respected by the medical profession until definitive proof is available. In a 1979 editorial in *JAMA*, Cousins said that "the connection between emotional and physical well-being seems obvious enough.... Yet, even as we perceive these connections, we lack solid information on the way the positive qualities [of emotions] make their physiological registrations."[7]

The Immune and Nervous Systems

As discussed in my essay on the 1984 Nobel Prize winners in medicine, all of whom were immunologists, the immune system is immensely complex and scientists have yet to unravel exactly how it works.[8] Two types of immunologic responses, mediated by two types of lymphocytes (white blood cells), have been found. Humoral immunity occurs when B lymphocytes produce immunoglobulins, called antibodies, that either destroy antigens (foreign structures) or mark them for destruction by other cells. T lymphocytes are involved in cell-mediated immunity. Some T lymphocytes act as killer cells that attack foreign or cancerous cells directly. These are the cells that cause rejection of organ transplants, but they are also a crucial line of defense against tumors. Other T lymphocytes interact with B cells to enhance or suppress their activity.[9]

The nervous system is an organized group of specialized cells, called neurons, that conduct information in the form of a stimulus impulse from a sensory receptor through a nerve-cell network to a response site. A neuron is constructed of three parts—dendrites, axons, and a cell body. The dendrites receive a stimulus impulse and pass it on to the cell body, which in turn passes it on to axons. Axons then secrete a chemical called a neurotransmitter (such as acetylcholine) that diffuses across a small gap until it reaches the dendrites of a nearby neuron. The neurotransmitter can either excite or inhibit the second cell.

The nervous system regulates the endocrine glands, ductless glands (such as the pituitary and thyroid) that regulate body processes by secreting chemicals known as hormones. These hormones travel through the bloodstream to specific target organs and tissues to promote or inhibit activity.[10]

The 1984 Nobel laureate Niels K. Jerne,[8] professor emeritus, Basel Institute for Immunology, Switzerland, made some interesting comparisons between the immune and nervous systems. He notes that "these two systems stand out among all other organs of our body by their ability to respond adequately to an enormous variety of signals. Both systems display dichotomies and dualisms. The cells of both systems can receive as well as transmit signals. In both systems the signals can be either excitatory or inhibitory. The two systems penetrate most other tissues of our body...[and they both] learn from experience and build up a memory that is sustained by reinforcement."[11] Jerne further proposes that these analogies may arise from similar genes that govern the expression and regulation of the two systems.

Anatomical and Chemical Pathways

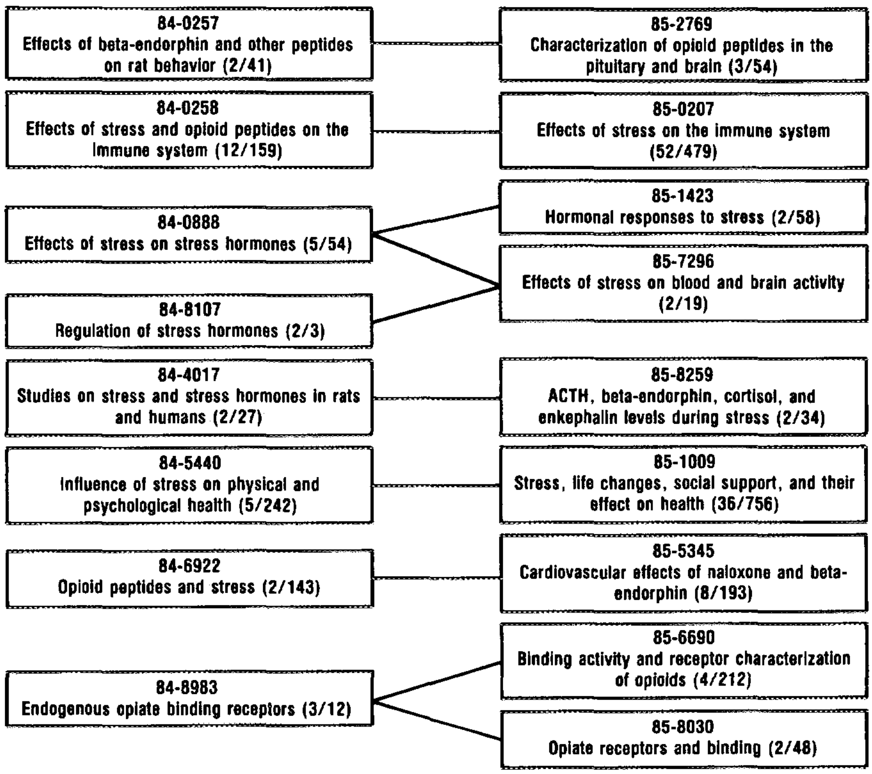
Similar as they may be, the exact manner in which the immune system and nervous system interact is still unknown. However, the evidence for anatomical and chemical connections between the two is accumulating rapidly. David L. Felten, Department of Neurobiology and Anatomy, University of Rochester School of Medicine and Dentistry, New York, and colleagues have shown that there are nerve endings in the various organs and tissues of the immune system, such as the spleen, lymph nodes, bone marrow, gut-associated lymphoid tissue, and thymus. Felten proposes that nerve terminals anatomically positioned among fields of lymphocytes may provide a means for the brain to speak directly to the cells of the immune system.[12] (Incidentally, Felten was mentioned previously as a 1982 winner of the MacArthur Prize Fellow Award.[13]) Pathologist Kathryn Miles, University of Chicago, and colleagues found that this anatomical pathway is a favorable environment for direct neural regulation of the immune system. They demonstrated that local destruction of nerve endings leads to immune alterations in antibody response.[14]

Not only can the nervous system regulate the immune system, but immune cells and organs can also influence neuronal activities. Hugo O. Besedovsky, Adriana del Rey, and Ernst Sorkin, Swiss Research Institute, Davos, have shown that the firing rate of brain neurons is altered by immune cell products, such as interferon and the interleukins, which regulate immune cell development and function.[15]

Researchers have long recognized that stress may produce immune suppression via the hypothalamus-pituitary-adrenal pathway. In stressful situations, the hypothalamic region of the brain produces corticotropin-releasing factor, which triggers the release of adrenocorticotropic hormone (ACTH) by the pituitary gland. The ACTH in turn stimulates the adrenal glands to secrete corticosteroid hormones, which cause immune suppression.

It has become clear, however, that this mechanism is not complete. Recently microbiologist J. Edwin Blalock, University of Texas Medical Branch, Galveston, has found that this pathway can be extended to include the immune system. He found that viral infections and certain toxins can directly induce lymphocytes to make ACTH.[16] These findings suggest that it is possible for the immune system to trigger the production of the immunosuppressant corticosteroid hormones directly. The Blalock paper on "The immune system as a sensory organ" cites into the core of a 1984 ISI® research front on the "Effects of stress and opioid peptides on the immune system"

Figure 1: Historiograph of research in the field of psychoneuroimmunology. The numbers given in parentheses following the research-front title refer to the number of core/citing items for each research front.



(#84-0258). This topic is one of eight 1984 research fronts we identified by co-citation clustering. Figure 1 is a historiograph showing how these and nine new fronts for 1985 related to psychoneuroimmunology are linked.

In other studies, Candace B. Pert, National Institute of Mental Health, Bethesda, Maryland, Michael R. Ruff, National Institute of Dental Research, and colleagues have discovered that neuropeptides, chemicals in the brain, may attract immune cells called macrophages to the site of injured tissue. Neuropeptides act as chemical messengers between nerve cells, regulating pain control, thirst, appetite, pleasure, and emotion. Pert and colleagues found that macrophages can secrete and functionally respond to various neuropeptides at the site of damaged tissue, where they scavenge bacteria and other debris that cause injury.[17]

Among the substances that elicit a macrophage response are benzodiazepines, a class of antianxiety drugs that includes Valium and Librium.[18] Other neuropeptides include the opiates, the pleasure-producing class of drugs that includes heroin and morphine. Pert hypothesizes that neuropeptides and their receptors are a key link between the mind and body since they may represent the biochemical foundation of emotion.[17,19] In the research front labeled "Endogenous opiate binding receptors" (#84-8983), two of the three core papers are coauthored by Pert and Solomon H. Snyder, Department of Psychiatry and the Behavioral Sciences, Johns Hopkins

University School of Medicine, Baltimore, Maryland.[20,21]

Stress and the Immune Response

In addition to these findings of anatomical and chemical pathways, many experiments have been done on the effect of stress on animals. While most results show that stress clearly influences the animal's immune system, scientists are wary about making conclusive statements about the implications of these results since there are so many variables that need to be experimentally controlled. These variables include the exact nature of the stress, the timing of its application to a particular organism, and the genetics of the test animal. In addition, Malcolm P. Rogers, Division of Psychiatry, Peter Bent Brigham Hospital, Boston, Massachusetts, and colleagues warn that there are many measures of immunity. For example, when studying immunosuppression, it is necessary to recognize that blocking suppressor T lymphocytes from functioning may actually augment other components of the immune system.[22]

In a letter to *Lancet*, J.G. Hall, Section of Tumour Immunology, Institute of Cancer Research, Royal Cancer Hospital, Surrey, UK, argues that lymphocyte proliferation is variable in healthy subjects and should not be used as a measure of immunological competence.[23] These complexities, in combination with our relatively limited knowledge of the immune system, require cautious evaluation of any data suggesting changes in immunity after psychological stress.

Nevertheless, a large number of animal experiments have identified some of the major variables and interactions that determine stress effects on health. In a landmark study in 1975, Ader, mentioned earlier, and immunologist Nicholas Cohen, both of the University of Rochester School of Medicine and Dentistry, were able to condition rats to suppress their own immune responses. Ader and Cohen gave laboratory rats a saccharin solution and 30 minutes later injected them with the immunosuppressive drug cyclophosphamide, which causes nausea. The single pairing of saccharin and cyclophosphamide caused rats to avoid drinking the saccharin to prevent feeling sick. During the course of repeated exposures to saccharin without cyclophosphamide, some conditioned animals died. The mortality rate was directly related to the volume of saccharin consumed in the single conditioning trial. It was hypothesized that reexposure to the saccharin without the immunosuppressive cyclophosphamide resulted in a conditioned immunosuppressive response that increased the animals' susceptibility to pathogens in the laboratory environment. Ader and Cohen then set up a similar experiment in which animals were immunized with sheep red blood cells (SRBC), and when conditioned animals were reexposed to saccharin, they showed a conditioned suppression of the antibody response to the SRBC antigen.[24]

Possible clinical applications for immunosuppressive conditioning may be in treating people with autoimmune diseases, such as rheumatoid arthritis or lupus, in which the immune system begins attacking the body's own tissues. This study is 1 of 52 core documents we identified for the "Effects of stress on the immune system" (#85-0207). (See Figure 1.) There were over 450 papers that cited 1 or more of these core papers in 1985. In terms of publication activity, this was surpassed by the front on "Stress, life changes, social support, and their effect on health" (#85-1009) with over 750 papers.

While it is apparent that illness is affected by the mental frame of mind, there are conflicting results as to whether stress suppresses or enhances the immune response. For example, Solomon, mentioned earlier, found that only certain types of stress are immunosuppressive. Overcrowding stress in rats was very effective in reducing the antibody response to an injected antigen. However, rats subjected to sleep-deprivation tests did not activate immunosuppressive mechanisms.[25]

Psychologists Lawrence S. Sklar and Hymie Anisman, Carleton University, Ottawa, Canada, examined the effects of coping with stressful situations on tumor development in mice. They found that the animal's degree of control over an event influences tumorigenicity. Mice subjected to inescapable shock developed larger tumors at a faster rate and died sooner than the mice subjected to escapable shock.[26]

Psychologists Mark L. Laudenslager, University of Denver, and colleagues took these studies one step further when they studied the immunological changes that occurred when animals were subjected to controllable and uncontrollable stressors. Laudenslager and colleagues measured how readily the T lymphocytes reacted when brought into contact with a mitogen, a substance that stimulates proliferation. The authors found that T lymphocytes from rats able to escape the shock multiplied as readily as did those from unstressed rats, while the T lymphocytes from rats exposed to inescapable shock did not multiply at a normal rate. It would seem that the degree of stress controllability, rather than the stress itself, may be a factor related to immunosuppression.[27]

Human Studies

Many clinical studies have focused on the effects of stress on immune responses in humans. Psychiatrist Steven J. Schleifer, Howard Mack Laboratory, Mount Sinai School of Medicine, New York, and colleagues studied the possibility that immunity may be altered as a result of bereavement. The authors compared lymphocyte stimulation responses in husbands before and after the deaths of their wives. The ability of lymphocytes to multiply was significantly lower two months after bereavement compared to the prebereavement levels. These changes in the immune system following bereavement may be related to the observed increased mortality of bereaved spouses.[28] The cited paper on "Suppression of lymphocyte stimulation following bereavement" is one of 12 core papers for research front #84-0258, mentioned earlier.

While bereavement is a severe stress, even milder forms may reduce immune responses in humans. Psychiatrist Janice K. Kiecolt-Glaser, Ohio State University College of Medicine, Columbus, and colleagues studied the effect of medical school exams on many immunologic parameters, including natural killer-cell activity.[29] Natural killer cells are programmed to prevent tumor development and spread. The immunological changes included a reduction in the T lymphocytes needed to mount an effective immune response and lowered natural killer-cell activity. In addition, many students were given the UCLA Loneliness Scale, discussed recently in the essay on loneliness.[30] Those with high scores also showed depressed immune activity even before the exams. The authors suggest that the immunosuppression associated with bereavement may be in part a function of the loneliness that accompanies the loss of a loved one. Kiecolt-Glaser's study is a citing paper associated with #84-0258 because it refers to the Solomon[25] and the Sklar-Anisman studies[26] mentioned earlier.

Allergies

As discussed in a previous essay, allergies are thought to be influenced by stress.[31] Briefly, allergies are mediated by the IgE immunoglobulin. These IgE have an affinity for immune cells called mast cells and attach to them to form an IgE-mast cell product. When an allergen enters the body, it reacts with the IgE-mast cell product, causing the mast cell to release chemicals that mediate the allergic reaction. These chemicals include histamine, which causes itching and flushing of the skin as well as smooth-muscle contraction in the bronchi of the lungs, causing difficult breathing.[9] Solomon conducted a study with Alfred A. Amkraut, Alza Research, Palo Alto, California, in which they observed that stress increases these IgE levels, which are known to be elevated in patients with asthma and other allergic diseases.[32]

In other allergy studies, Michael Russell and colleagues, Brain-Behavior Research Center, Sonoma Developmental Center, University of California, Eldridge, used a classical conditioning procedure to pair an agent that provokes the immune system with the presentation of an odor to guinea pigs. When the odor was presented alone, there was an increase in the histamine level, suggesting that the immune response can be triggered by associative learning. This report may account for many anecdotal reports of allergic reactions, such as the asthmatic patient allergic to roses who experiences an asthma attack when exposed to an artificial rose.[33]

Controversy

While these research findings seem compelling, psychoneuroimmunology is not without its share of controversy. Studies have been published that show no correlation between psychological factors and disease. In a study published in the *New England Journal of Medicine*, Barrie R. Cassileth and colleagues from the University of Pennsylvania Cancer Center, Philadelphia, found that such factors as life satisfaction, ability to cope with cancer diagnosis, and the degree of hopelessness of 359 cancer patients did not affect their recovery rate.[34]

In the same journal issue, deputy editor Marcia Angell wrote a controversial editorial warning that too much emphasis on mind control of disease may cause patients to consider traditional medical care as unnecessary. She adds that "a view that attaches credit to patients for controlling their disease also implies blame for the progression of the disease." Angell points out that patients already burdened by disease should not be made to feel responsible if they are unable to recover.[35]

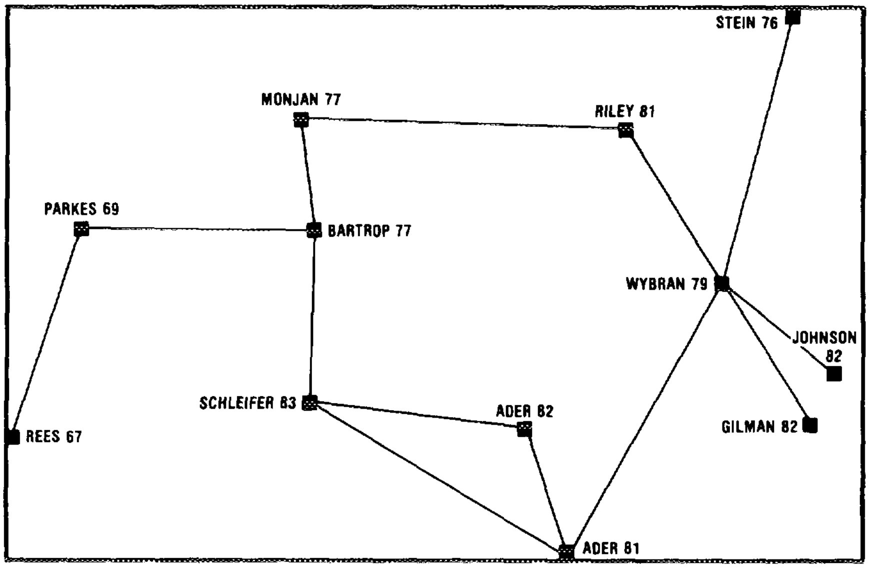
These same arguments have traditionally been directed toward such controversial fields as faith healing and the religion of Christian Science. Followers of Christian Science believe that Christ's healing works and his resurrection demonstrate that the limitations of the mortal state, such as illness and death, can be overcome as one gains "the mind of Christ"—a rooted understanding of one's true spiritual status. Accordingly, one of the tenets of Christian Science is that faith, not medical treatment, is the key to health and healing.[36]

Current research has already established a physical brain-body connection. Future research will need to grasp just how that link operates before the controversies surrounding psychoneuroimmunology can be fully resolved. Until that time, attempts are being made to conduct controlled studies of spiritual healing in rheumatoid arthritis.[37]

Psychoneuroimmunology Literature

Despite Angell's arguments, there are numerous studies confirming a relationship between the mind and body that cannot be ignored. Indeed, for a field that has emerged fairly recently, there is a considerable body of literature that is growing rapidly. In the research front on the "Effects of stress, psychosocial factors, beta-endorphins, and other opioid peptides on the immune system" (#84-0258), there were 12 core documents. These documents are arrayed in a multidimensional-scaling map in Figure 2 showing how these papers are linked. This front is linked to the 1985 front on the "Effects of stress on the immune system" (#85-0207), which has 52

Figure 2: Multidimensional-scaling map for C1-level research front #84-0258, "Effects of stress, psychosocial factors, beta-endorphins, and other opioid peptides on the immune system," showing co-citation links between core papers. See key for bibliographic data.



Key

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Ader R & Cohen N. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science* 215:1534-5, 1982.
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core documents, demonstrating the growth of the literature in this field. Nine of the core papers from #84-0258 carry through into #85-0207, including the paper by Schleifer and colleagues[28] and Ader's book *Psychoneuroimmunology*.[1]

Table 1 lists the major journals in which research articles on psychoneuroimmunology occur most frequently. This table was developed using keywords, concepts, and prominent authors in an online and manual literature search to develop a preliminary journal list. We examined core and citing papers from the current relevant research fronts. The journals that appeared most often were added to the preliminary list. The final list has been carefully edited to provide an inclusive representation of all facets of psychoneuroimmunology research.

In his book *Psychoneuroimmunology*, Ader compiled a scholarly yet readable series of articles from the leading researchers in the field.[1] Twenty-six contributors, including Besedovsky, Schleifer, and Solomon, provide a comprehensive collection of scientific results pointing to a definite link between the brain and many immunologic processes. In addition, Ader is the editor of a new Academic Press journal, *Brain, Behavior, and Immunity*, scheduled to appear early in 1987.

The Institute for the Advancement of Health has published three comprehensive reviews, all edited by psychiatrist Steven E. Locke, Harvard Medical School. The first volume, *Mind and Immunity: Behavioral Immunology*, provides bibliographic references and abstracts of 1,400 papers.[38] *Psychological and Behavioral Treatments for Disorders of the Heart and Blood Vessels* contains accounts of 916 papers dealing with psychological factors and cardiac diseases.[39] *Psychological and Behavioral Treatments for Disorders Associated with the Immune System* contains over 1,450 entries from journals and books published between 1848 and 1985.[40]

Conclusion

Understanding how the immune system and the nervous system interact may influence the method of treatment for many diseases, including cancer. Influencing the chemical messages sent from the brain to the immune system (or vice versa) may prove to be an effective form of therapy in the near future.

Table 1: List of journals that report on research and advances in psychoneuroimmunology. A = title. First year of publication is given in parentheses. B = 1984 impact factor.

A	B
Biological Psychiatry (1969)	2.22
Brain Research Bulletin (1976)	1.87
Cellular Immunology (1970)	2.45
Clinical and Experimental Immunology (1966)	2.71
Clinical Immunology and Immunopathology (1972)	2.46
Endocrinology (1917)	4.34
Journal of Human Stress (1975)	.50
Journal of Personality and Social Psychology (1965)	1.75
Journal of Psychosomatic Research (1956)	.83
Psychological Bulletin (1904)	3.43
Psychoneuroendocrinology (1976)	1.36
Psychosomatic Medicine (1938)	2.83
Psychotherapy and Psychosomatics (1953)	.82
Zhurnal Nevropatologii i Psikhiatrii imeni S S Korsakova (1901)	.28

This emerging field has broken new ground in the medical world, causing physicians to develop new respect for the complexity and recuperative capacity of the brain and immunological interaction. In a 1976 article in the *New England Journal of Medicine*, Norman Cousins gives hope for the future prospects of psychoneuroimmunology research when he writes that "the life-force may be the least understood force on earth. William James said that human beings tend to live too far within self-imposed limits. It is possible that those limits will recede when we respect more fully the natural drive of the human mind and body toward perfectibility and regeneration."[41]

* * * * *

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