

Mind and Immunity—The Growing Field of Psychoneuroimmunology. Is It Fact or Folklore?

DIANE E. SCHULLER, M.D. and DOLORES E. RODRIGUEZ, M.D.

ABSTRACT

There is significant integration of the central nervous system and immune system. Now, increasing evidence supports the role that stress plays in the development of certain disease states. Medical management must therefore include consideration of the patients' life-style, adaptation, and health.

INTRODUCTION

THE CONCEPT THAT STRESS AND DISEASE are related has long been a subject of controversy. The importance of determining if possible relationships exist between stress and the onset of certain illnesses is obvious. In an editorial "Disease as a Reflection of the Psyche" that appeared in the *New England Journal of Medicine* in June 1985, Dr. Marcia Angell stated that the evidence was not convincing that the mental state is a major factor associated with the causation of specific diseases. She noted that the popular media has cautioned us as to the hazards of certain personality types and concern has been raised that cancer is more likely to occur in unhappy people. There is danger, she noted, in raising the hopes of patients that their attitudes could save them from disease. She further stated that people who are ill may blame themselves and may feel guilty if they get worse. The basic assumption that controlling attitudes and feelings allows patients a sense of control over their disease was questioned, and Dr. Angell believed it could possibly even be harmful⁽¹⁾

Following this editorial, the debate greatly intensified on the issue of attitude and health. Daniel Goleman of the American Psychological Association issued a statement in *The New York Times* (October, 1985) denouncing the editorial as "inaccurate and unfortunate," ignoring important research findings. He stated that no one believes that cancer directly results from becoming depressed, but emotions do contribute to the onset and course of the disease.

Department of Pediatric Allergy, Immunology and Pulmonary Diseases, Geisinger Medical Center, Danville, Pennsylvania.

Supporters note strong evidence linking the brain, the immune system, and the course of disease. Everyone agrees that positive attitudes are not a substitute for competent medical attention; however, many feel that emotions can be an important additional weapon in fighting illness.⁽²⁾

To review this issue objectively, one first must examine the basic premise that stress may increase an organism's vulnerability to certain diseases by means of exerting an immunosuppressive effect. This should be of note in those diseases associated with immunological mechanisms such as infection, malignancy, autoimmune disease, and even allergy. If these suspicions are true, that the mind can influence disease through immune function, certain postulates need to be examined and evidence gained for their support. These postulates include the following: (1) Central nervous system (CNS)-controlled hormones (neuroendocrines) should regulate immune systems. (2) Receptor sites for neurohormones should be present on immune-modulating cells. (3) The immune response should be affected by experimental alteration of parts of the CNS. (4) Immunologic abnormalities should occur in patients with emotional and mental disorders. (5) Abnormal emotional states should affect the frequency of diseases in which natural host immunological resistance exists and be present in immunodeficiency states. (6) Changes in the immune system should be noted following behavioral modification (i.e., conditioning).

It is important to realize that in studying such possibilities, there are natural variables in immune function that need to be recognized. For example, there is diminished humoral immunity in infants and diminished humoral immunity as well as cellular-mediated immunity in the elderly. The elderly also have an increased incidence of autoantibody formation in addition to malignancy. In a prospective study of individuals over 80 years old, there was a significant correlation between decreased cellular-mediated immunity and increased mortality.⁽³⁾ Lymphocytes of the elderly appeared to produce less interleukin-2 (IL-2). It is also important to realize there is diminished cell-mediated immunity during pregnancy which allows for protection of the fetus.⁽⁴⁾ There are even variables according to sex and race, with females having 20% more IgM than males and blacks having higher IgG levels.⁽⁵⁾

Last, diurnal variations and circadian rhythms exist that influence immune functions, including secretory IgA, plasma cell immunoglobulin response to antigen stimulation, quantitative levels of circulating lymphocytes, and response to mitogenic stimulation.⁽⁶⁾ Hormones have 24-hour secretion rhythms that could influence immune mechanisms (for example, transformation of lymphocytes *in vitro* by mitogens vary directly with cortisol rhythms).⁽⁷⁾ Diurnal variations in natural killer cell activity have also been reported.⁽⁸⁾ Therefore, the timing of stress in relation to naturally occurring rhythms may influence the immunological consequences.

Let us examine our first postulate to see if mechanisms exist by which the CNS may have an influence on immune function. Hypothalamic-pituitary hormonal stimulation appears to play an important role. Besedovsky⁽⁷⁾ noted that increased neuronal firing in the hypothalamus occurred after antigen-antibody interaction in the rat but prior to any change detected in hormone levels. This observation provided a suggestive link between the immune reaction and the CNS. Subsequently, it was shown that the hypothalamus, rich in neural connections to the limbic system, has receptors for humoral influences from the blood and CNS and influences the pituitary by release of neurohormones and neurotransmitters with subsequent modulation of cellular and humoral immunity.⁽⁹⁾

Several studies on the hypothalamus have given us important evidence. Lesions placed in the anterior basal area of the hypothalamus prevent lethal anaphylactic shock in the guinea pig when placed prior to sensitization but not following sensitization.⁽¹⁰⁾ Lesions in the hypothalamus will suppress the Arthus reaction in the rat, while stimulation of the hypothalamus will enhance the Arthus reaction.^(11,12) Destruction of the dorsal part of the hypothalamus will decrease primary antibody responses, while stimulation of the dorsal area will increase primary antibody responses.^(13,14) Posterior hypothalamic lesions worsen allergic polyneuritis and may reflect an absence of antibody to myelin that plays a protective role.⁽¹⁵⁾ Anterior hypothalamic lesions will decrease cell-mediated immune response to tuberculin, while stimulation of the anterior hypo-

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thalamus will increase cell-mediated immune response.^(16,17) There is no change in the absolute number or percentage of T and B cells observed; however, there is decreased stimulation *in vitro* of lymphocytes by phytohemagglutinin and tuberculin. Last, following antigen exposure (i.e., immunization), the firing rates of neurons of specific nuclei of the hypothalamus increase, suggesting a feedback loop between the immune response and hypothalamus.⁽¹⁸⁾

The neuroendocrine systems' release of physiological amounts of various hormones is essential for immune development and function (i.e., corticosteroids, thyroid hormone, insulin, growth hormone, and sex hormones).⁽¹⁹⁾ The direction of this effect is dose related.⁽²⁰⁾ For example, high doses of steroids are immunosuppressive whereas physiological levels are necessary for normal functions of immunity. It is well known that corticosteroids have a major effect upon immune function. The majority of their action results from decreased IL-2 production and a subsequent lack of proliferation of sensitive lymphocytes.⁽²¹⁾ Corticosteroids affect T-cell distribution and population. With decreased T-cell-mediated immunity, the effect upon antigen is greater than nonspecific mitogen. There is a decrease in the mixed leukocyte reaction,⁽²²⁾ and monocyte and macrophage distribution and activation are also affected.⁽²³⁾ Natural killer cell activity is diminished through the effects of corticosteroids, and it is known that these cells play an important role in tumor immunity.⁽²⁴⁾ Neutrophils are likewise affected by corticosteroids with decreased lysosomal release and decreased bactericidal activity being observed. Decreased monocyte chemotaxis is further noted.⁽²⁵⁾

It is well known that responses to stress include stimulation of the hypothalamus with the resultant response noted in the adrenal medulla followed by the release of catecholamines, which in turn release many other hormones including glucocorticoids, growth hormone, adrenocorticotropin, and so forth.⁽⁹⁾ In support of our second postulate, lymphocytes have receptors for β -adrenergic catecholamines, which increase cyclic AMP and are immunosuppressive. Therefore, increased catecholamine levels observed with stress should have an immunosuppressive effect.⁽²⁶⁾

The autonomic nervous system likewise responds to stress through an inhibitory effect observed on cell-mediated immunity. There is a direct innervation of the spleen and thymus. In a recent Japanese study, suppression of the primary immune response was observed after chemical sympathectomy.⁽²⁷⁾ Last, opioid peptides, which include endorphins, enkephalins, and dynorphins, are released during stress and are immunomodulators. Lymphocytes have opioid receptors which suppress the immune response, as demonstrated in studies by Lewis.⁽²⁸⁾ Chemicals that block opiate action also keep uncontrollable stressors from suppressing the immune response.

Therefore, it is evident that the CNS's control of the hypothalamus has a direct effect upon the autonomic nervous system, pituitary, and lymphoid tissues, which in turn affect the release of neurohormones and neurotransmitters that have a direct effect on the immune system. Thus, the basis for stress on the CNS having a direct effect upon immunity does exist.

Perhaps it is important first to define our concept of stress. Generally it is accepted as the "perception of threat to physical or psychological well-being and the perception that responses are inadequate to cope with it."⁽²⁹⁾ Stress represents an extraordinary demand on physiological or psychological defenses with concomitant responses of the neuroendocrine systems to the external elicitor. Psychosocial and physical stress may be interrelated (for example, starvation and overcrowding). One must remember that behavior responses to stress are complex and the response to stress may also have an influence upon immune response. For example, an individual may start to abuse drugs, alcohol, or cigarettes or have changes in diet, sleep, and waking behavior—all of which may have a direct effect upon the immune response itself.

To address our third postulate, let us first examine the effects of stress in animals. Interestingly, adrenalectomized rats exhibited no stress-related decrease in lymphocyte numbers after shock therapy, whereas lymphopenia was noted in nonoperated or sham-operated animals. However, stressful conditions suppress the stimulation of lymphocytes by PHA in adrenalectomized as well as nonoperated animals. Hence, stress-related secretion of corticosteroids and

catecholamines is not required for stress-induced suppression of the lymphocyte stimulation by PHA. This is fascinating and may be due to changes in subpopulations or redistribution of T cells by adrenal-independent mechanisms, which further emphasizes the fact that stress-induced modulation of immunity is complex, involving several, if not multiple, mechanisms.⁽³⁰⁾ Numerous animal studies have examined closely the impact of various kinds of stress, such as shock avoidance, confinement, exposure to predator, and electric shock. These have been shown universally to cause adrenal hypertrophy, decreased circulating lymphocytes, decreased size of the thymus and spleen, and increased severity of viral infections.⁽⁹⁾ Crowding of animals has also been shown to increase mammary tumors (92% tumor rate in mice with overcrowding when a normal 7% rate is seen in nonstressed mice⁽³¹⁾). Even sound-induced stress has caused decreased granuloma formation with an effect upon cell-mediated immunity.⁽³²⁾ Starvation has produced significant decreased graft versus host reaction, but the stress must be applied during the first 3 days of transplantation. Therefore, timing once again is important. To emphasize this fact further, Flagellin immunization produced higher primary and secondary antibody titer responses in stressed (handled) infant rats versus a control group. However, if stress was applied 1 week prior to immunization, a decreased antibody response was noted.⁽³³⁾ Again, timing is crucial.

In summary, with animal studies it appears that the nature of the stress, timing of the application (i.e., life cycle stage, diurnal rhythmicity, and genetics of the host) are all important factors. Stress is associated with diminished cell-mediated immunity reflected in decreased skin homograph rejection in mice, decreased graft versus host responsiveness, and decreased delayed hypersensitivity reactions.

Stress responses in man have been examined and are even more fascinating. Recent life changes (i.e., stress) do appear to increase the likelihood of disease at a level that is statistically significant but by no means uniformly associated with disease. Stress obviously has a complex interaction with the personality and biology of the host and hence with the expression of disease. The role of social support appears to be quite important. If social support is high, a protective effect is noted. If it is low, the effects of stress are magnified.^(34,35)

In examining our fourth and fifth postulates, bereavement is perhaps one of the most potentially stressful of the commonly occurring life events. Prospective studies have been done that greatly demonstrate this fact. In a study of males ages 55–74, a significant increase in the risk of mortality was noted in widowed males compared to married men or widowed women.⁽³⁶⁾ In another study, spouses of breast cancer patients showed decreased lymphocyte mitogen response for the first 2 months following bereavement. During the first year following the death of the spouse, most recovered but not all.⁽³⁷⁾ In another study, decreased IgG and IgA levels were noted during the bereavement period in family members.⁽³⁸⁾ CNS-mediated stress effects have been proposed as a mechanism associated with depression or anxiety that may occur during the bereavement period. One also must realize that life-style changes occur during the bereavement period, namely changes in nutrition, activity, levels of exercise, periods of sleep, or even drug use. Any of these latter factors could affect lymphocyte function and hence affect immunity.

Studies addressing some of these latter life-style changes have been done. Increased interferon production and biphasic changes in phagocytic activity were observed during a 77-hour sleepless vigil.⁽³⁹⁾ Moldofsky⁽²¹⁾ correlated sleep stages of six healthy males with changes in cortisol levels, IL-1 and IL-2 activity, natural killer cell activity, and mitogen response. He noted a dramatic change in immune activity, with increased IL-1 activity occurring at midnight, followed 30 minutes later by increased IL-2 activity. Between 1:00 and 3:00 a.m. there was a decrease in natural killer cell activity, whereas there was an increased lymphocyte response to pokeweed mitogen noted between midnight and 7:00 a.m. Cortisol plasma levels, of course, decreased during sleep.⁽²¹⁾ Phagocytosis of *Staphylococcus aureus* by neutrophils has been reported to be diminished after sleep deprivation.⁽³⁹⁾ These are certainly important implications concerning the relevance of sleep to the restorative biologic processes of individuals and normal physiologic homeostasis.

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Nutrition is another factor that is extremely important in maintaining immune function. Malnourished children have been noted to have an increase in viral and Gram-negative infections.^(40,41) Children with Kwashiorkor have had diminished tuberculin reactions and have failed to develop a positive TB test after BCG immunization.⁽⁴²⁾ With protein calorie malnutrition (levels of albumin less than 3.5), decreased cell-mediated immunity has been reported.⁽⁴³⁾ In a study of 21 adults receiving parenteral fluids for trauma, there was a decrease in the number of circulating lymphocytes as well as decreased *Candida* and DNCB responsiveness. However, it is difficult to state whether these effects were secondary to increased cortisol levels that may have followed the stress of trauma.⁽⁴⁴⁾

Exercise has been noted to have a role in immune function. Running a marathon was reported to be associated with decreased lymphocyte activity. This may be a result of increased catecholamines, corticosteroids, or even the effects of endorphins.⁽⁴⁵⁾

Drug use is known to have an effect upon immunity. Alcohol abuse has been associated with decreased cell-mediated immunity and antibody responsiveness.⁽⁴⁶⁾ Chlorpromazine and some antibiotics have been associated with decreased cell-mediated immunity and antibody response. Psychotropic agents such as phenothiazines have been shown to affect T-cell blastogenesis.^(47,48) Therefore, it is conceivable that an individual who experiences stress-related life-style changes and resorts to the use of drugs could further affect his/her immune system.

As previously mentioned, the role of social support is extremely important. Kiecolt-Glaser⁽⁴⁹⁾ examined loneliness, stressful life events, urinary cortisol levels, and immunocompetency in 33 nonpsychotic patients. Patients who scored above the median on the loneliness scale showed increased urinary cortisol levels, decreased natural killer cell activity, and decreased responsiveness to phytohemagglutinin. Hence, T-cell abnormalities noted in bereavement may be a reflection of poor social support and increased loneliness.⁽⁴⁹⁾ In another study by Thomas,⁽⁵⁰⁾ 265 elderly individuals (ages 61–89) who exhibited strong social interaction and emotional status had lower uric acid levels, lower cholesterol levels, higher total lymphocyte counts, and higher mitogen responsiveness than did individuals exhibiting poor social support.⁽⁵⁰⁾

Coping is also an important factor to evaluate. Several excellent studies have reported the relationship between coping and immune responsiveness. In 1985, Glaser reported on 49 first-year medical students who had Epstein-Barr virus (EBV), herpes simplex virus (HSV), and cytomegalo virus (CMV) titers obtained 1 month before exams, the first day of examination, the first week after exams, and during vacation. Subjects were divided according to the median split on the UCLA loneliness scale into individuals with high- and low-scoring loneliness groups. Those who scored the lowest levels (least stressed individuals) had no significant change in antibody titers to any of the three viruses, whereas those who scored high on the loneliness scale had significant changes in viral titers. Therefore, stress could certainly modulate HSV latency.⁽⁵¹⁾ In another study by Locke, who examined 114 Harvard undergraduates, coping abilities were correlated with natural killer cell activity. He correlated self-reported life-change stressors and psychosomatic symptoms with natural killer cell activity. Those individuals who exhibited few psychosomatic symptoms in the face of large amounts of life-change stressful events were defined as good copers, whereas poor copers exhibited anxiety and depression with stress. Interestingly, good copers had significantly higher natural killer cell activity than did poor copers.⁽⁵²⁾ Another study of 64 first-year dental students, found that secretory IgA secretion rate was diminished with stress and recovery was decreased in inhibited, power-driven individuals.⁽⁵³⁾ Last, in a study by Ressler, subjects who were rated high in ego strength had significantly greater antibody responsiveness to influenza vaccine than did poor-ego-strength individuals. Hence, coping certainly can affect antibody responsiveness.⁽⁵⁴⁾

Depression has a significant effect on decreasing the number and functional activity of lymphocytes that has been related to the severity of depression. Altered immunity has been reported in patients with major depressive disorders who are hospitalized, while it has not been reported in those who are ambulatory (obviously less depressed) or in normal controls. The

depression is not secondary to hospitalization itself, because no decreased immunity has been noted in hospitalized schizophrenics. It has been postulated that the alterations in immune function may be related to a neurotransmitter defect occurring in depression. Hypersecretion of cortisol has been noted in some depressed individuals. Decreased immune function may also be a result of a deficiency of norepinephrine, which has a tonic inhibitory effect on ACTH and cortisol secretion.⁽⁵⁵⁾

Susceptibility to infection has been examined closely in numerous studies. Obviously, even among susceptible individuals, only a fraction of those infected with a pathogen actually develop a full clinical illness. Ishigami⁽⁵⁶⁾ first reported on the effects of stress and decreased phagocytic activity during periods of "emotional excitement," which he attributed to the changes and stresses of contemporary life. In 1957, Holmes noted increased life changes reported in those individuals requiring frequent hospitalizations for tuberculosis.⁽⁵⁷⁾ An increased frequency and duration of infections has been reported with stressful family situations (children and college students) as well as male prisoners.⁽⁵⁸⁻⁶⁰⁾ Stress appears to impair immunologic function. In two studies, a nasal spray containing rhinovirus caused significantly more symptoms in patients with high stress levels.^(61,62) In a prospective study of patients with HSV-1 recurrences, there was a marked increase in frequency of occurrences noted when individuals were unhappy. Daily mood scores were obtained in these individuals and depression clearly preceded a flare of the HSV infection and increased antibody titer.⁽⁶³⁾ Maternal deprivation has also been reported to increase susceptibility to infection. Spitz noted increased morbidity and mortality secondary to increased susceptibility to infection in institutionalized children not visited regularly by their mothers.⁽⁶⁴⁾ Laudenslager reported on 6-month-old monkeys who were separated from their mothers. Two weeks later, a diminished immune response was noted with decreased lymphocyte proliferation.⁽⁶⁵⁾ Coe and Levine, in a similar study, noted a decreased ability to generate antibodies to specific viral invaders associated with maternal deprivation.⁽⁶⁶⁾ EBV infection and recovery studies have also been linked to stress. Greenfield⁽⁶⁷⁾ studied 38 college students with mononucleosis. Those with high scores for psychological health had a much more rapid recovery. Kasel and Evans⁽⁶⁸⁾ studied 1327 West Point cadets. They were screened prospectively for EBV titers. Those who were negative were followed for clinical development of mononucleosis or for asymptomatic seroconversion. Interestingly, those who became symptomatically ill had high levels of motivation but were poor academic performers and their fathers were classified as overachievers.⁽⁶⁸⁾

The susceptibility to infection obviously appears to be complex, with great variability in morbidity and mortality that can depend upon the nature of the pathogenic organism, the quantity and quality of stress, genetic factors, environmental factors (i.e., housing), and psychosocial factors such as support. Even in AIDS, depression has been associated with onset of the full-blown illness. Silberstein reported a major depressive illness 9-24 months before the onset of AIDS in 5 of 6 patients. In general, the patients felt helpless and reported that life stressors were out of control. It is possible that coping styles may correlate with an individual's vulnerability to AIDS and the expression of full-blown disease.⁽⁶⁹⁾

A great deal of interest has been raised regarding the relationship between the immune system, stress, and the development of cancer. Amussat first reported on the influence of grief, which he noted commonly related to the development of cancer.⁽⁷⁰⁾ Premorbid personality traits, coping styles, psychosocial stressors, and timing appear to be important. Once again, stress does not appear to be oncogenic; however, the inability to cope with stress may permit the development and proliferation of tumor cells. A prospective study⁽⁷¹⁾ on personality, coping skills, and the outcome of cancer had interesting results. Women with suspicious Pap smears underwent psychological testing noting recent loss or feelings of hopelessness. Using the psychological data, the investigators were able to predict with great accuracy which women would eventually develop full-blown cervical cancer.⁽⁷¹⁾

An individual's reaction to the development of breast cancer appears to have an effect upon survival. Women who express anger appear to have increased natural killer cell activity and

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increased survival rates compared with those who accept the disease and adjust to it.⁽⁷²⁾ Other studies appear to confirm the recurring theme of a history of a recent loss of a significant relationship prior to the development of cancer, unexpressed hostile feelings, or feelings of hopelessness and/or helplessness.⁽⁷³⁾ As mentioned, in animal studies, uncontrolled stress will cause increased tumor growth, decreased natural killer cell activity, and decreased T-cell multiplication. ⁽⁷⁴⁻⁷⁶⁾ In students, significant life changes and poor coping have been associated with decreased natural killer cell activity.⁽⁷⁷⁾ One would hope that our goal should be effective stress management, the development of healthy coping mechanisms, and restructuring of faulty psychological defenses that might allow an individual to resist better the development of cancer or help them fight the disease in a more effective fashion.

Autoimmune disease and its relationship to the immune system have also been examined (hyperthyroidism, rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, multiple sclerosis, and ulcerative colitis). Personality factors have been said to affect the severity and course of the illness; however, most likely the illness reflects a combination of genetic predisposition, psychological stressors, and poor adaptation to that stress.⁽⁷⁸⁾ The critical factor appears to be a lack of T suppressor cell function that results in autoantibody formation and the development of disease.⁽⁷⁹⁾ Studies have indicated that individuals with autoimmune disease appear to respond to stress with flares of their illness.⁽⁸⁰⁾

No specific personality factor has been associated with the development of asthma, although asthmatics have been thought in the past to have dependency conflicts.⁽⁸¹⁾ Stress certainly may be an aggravating factor in asthmatics because the autonomic nervous system does play a definite role in the control of bronchospasm and bronchodilation. There is an increased availability and release of mast cell mediators via cholinergic stimulation or the influence of neuropeptides.⁽⁸²⁾ Even learned histamine release has been demonstrated. Russell⁽⁸³⁾ performed an experiment using bovine serum albumin (an immunologic challenge) paired with the presentation of an odor (nonimmunologic challenge) in a guinea pig. Increased histamine release was observed. Subsequently, odor challenge alone caused histamine release. This demonstration suggested that an immune response could be enhanced by activity of the central nervous system. As far back as the 19th century, associative learning was noted in asthmatics. For example, an asthma attack associated with exposure to real roses was subsequently caused by exposure to artificial roses. Hence, associative learning should be included in understanding the development and treatment of allergic diseases.

Last, possibilities at modification have been examined and they confirm our sixth postulate. Behaviorally conditioned immunosuppression has been demonstrated that further links the connection between the psyche and the immune system. Ader performed an experiment in rats using saccharin (conditioned stimulus) plus cyclophosphamide; this resulted in gastrointestinal distress and immunosuppression. Subsequent challenge with saccharin alone also resulted in immunosuppression, as measured by decreased responsiveness to antigen stimulation and lower antibody titers raised to immunization with sheep red blood cell antigen. This immunosuppression was not a result of a nonspecific stimulus, because lithium was substituted for cyclophosphamide and no immunosuppression was noted. It also was not felt to be a result of increased corticosteroid levels, because increased levels were noted when both lithium or cyclophosphamide were used. The mechanism was felt to be T-cell dependent and suggestive of "recall of suppressive immunity" by the conditioned stimulus after the unconditioned stimulus of the immunosuppressive drug.⁽⁸⁴⁾

Other studies regarding modification have been done using tuberculin. Smith⁽⁸⁵⁾ noted that a delayed response to tuberculin was significantly decreased by psychological mediation. Seven positive tuberculin employees were skin tested monthly using saline (red vial) on one arm and tuberculin (green vial) on the other. On the last month, the contents of the vials were switched. Interestingly, all seven patients showed diminished erythema and induration (from 15 to 4 mm) in the tuberculin-tested arm at 6 months while the saline-tested arm remained negative. This

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certainly represented a manifestation of behaviorally conditioned suppression.⁽⁸⁵⁾ Black⁽⁸⁶⁾ noted that tuberculin reaction was inhibited by hypnotic suggestion. Although typical swelling and erythema were absent, skin biopsies did reveal the expected degree of cellular infiltration; however, there was a lack of responsiveness of the target organ—the capillary system.⁽⁸⁶⁾ Most recently, in a prospective randomized, controlled study of children ages 6–12 years old, learned self-hypnosis was demonstrated to regulate salivary IgA levels.⁽⁸⁷⁾

Hypnosis has also been examined in other studies, and inhibition of the immediate hypersensitivity reaction in allergic dermatitis, allergic responses to food, and urticaria has been observed. Meditation has been examined further by Smith⁽⁸⁸⁾ who noted altered delayed hypersensitivity responsiveness to varicella in a subject experienced in meditation. The altered delayed hypersensitivity reaction to repeated varicella antigen challenge was obtained by conscious visualization techniques. Obviously, there are individuals who can consciously control some degree of influence over their immune system.⁽⁸⁸⁾

As our six postulates appear to be satisfied, what are the implications for the future? The mechanism of infectious and neoplastic disease onset may be associated with various psychologic processes, such as hopelessness or depression. Once these can be understood better, perhaps intentional modulation could be used therapeutically to increase or decrease the immune response and alter the outcome.

In conclusion, it is important to remember one must always consider our patients' "state of mind" as part of their total health picture and consider the important role of coping and social support. Finally, for ourselves, on whom our families and patients depend so much, it is important to remember continually to try and minimize stress as much as possible. Perhaps it is indeed true that "laughter should be a part of the best medicine."⁽⁸⁹⁾

ACKNOWLEDGMENTS

We wish to express our appreciation to the staff of the Medical Library at the Geisinger Medical Center for their assistance in the extensive literature search and to word Processing for the typing involved in the preparation of this document. We would also like to thank Karen Younger for her assistance in the preparation of this manuscript.

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Address reprint requests to:
Diane E. Schuller, M.D.
Director, Department of Pediatric
Allergy, Immunology and
Pulmonary Diseases
Geisinger Medical Center
Danville, PA 17522

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1. Herbert C. Mansmann, Jr.. 1989. From Leeches to "Informational Substances" in 100 YearsFrom Leeches to "Informational Substances" in 100 Years. *Pediatric Asthma, Allergy & Immunology* 3:1, xvii-xviii. [[Citation](#)] [[PDF](#)] [[PDF Plus](#)]