Journal of Neuroscience Research 18:1-9 (1987)

Psychoneuroimmunology

Psychoneuroimmunology: Interactions Between Central Nervous System and Immune System

G.F. Solomon
Departments of Psychiatry, University of California, Los Angeles, and University of California, San Francisco, and Substance Abuse Treatment Unit, Sepulveda VA Medical Center, Sepulveda, California

Psychoneuroimmunology, a rapidly developing field, has to do with the complex bidirectional interactions between the central nervous system and the immune system. Neuroendocrine influences modulate immune function, and there is feedback from the immune system to the brain. CNS-immune interaction appears to play a role in psychosocial influences on immunologically resisted and mediated diseases. With the growing evidence now at hand, over 30 "postulates" can be proposed for specific implications of CNS-immune interaction.

Key words: *immunology, neuroimmunomodulation, behavioral immunology*

INTRODUCTION

In 1964, the year of the coining of the neologism "psychoimmunology"—later amended to "psychoneuroimmunology" by Ader [1]—a paper entitled "Emotions, Immunity and Disease: A Speculative Theoretical Integration" by Solomon and Moos [2] began as follows: "Recent advances in immunology, clarification of the psychophysiology of stress, continued progress in the discovery of emotional factors in relation to physical disease, and the finding of apparent immunological disturbances in conjunction with mental illness lead to this attempt at a theoretical integration of the relation of stress, emotions, immunological dysfunction (especially autoimmunity) and disease, both physical and mental." Exemplified by early reports of abnormalities of immunoglobulin levels in schizophrenic patients [3], a variety of immune aberrations, including autoantibodies, came to be found in conjunction with mental illnesses [4]. On the "other side of the coin," emotional and personality factors were being found to play significant roles in the onset and course of autoimmune diseases, particularly rheumatoid arthritis [5]. Autoimmunity, in turn, was being related to "relative immunologic incompetence" and the formation of antigen-antibody complexes [6]. It was clear that "stress" and emotional distress, such as bereavement and depression, were accompanied by elevation of adrenal cortical steroid hormones [7]. Adrenal corticosteroids were known to be immunosuppressive. Thus, simply, arose the first CNS-immune hypothesis: "Stress can be immunosuppressive."

I reported stress-induced suppression of primary and secondary immune response in rats in 1969 [8]. It was at about the same time and in the same laboratory that another experimental influence, early handling, was shown to have a lasting effect on humoral immunity, one of enhancement [9]. Ader and Cohen's [10] elegant immunopharmacologic experiments convincingly demonstrating that immune responses can be classically conditioned, as first discovered by Metal'nikov and Chorine in 1926 [11], most clearly implicated the CNS in the modification of immune responses. By 1975 immunity could no longer be considered an "autonomous" agency of defense against infectious and neoplastic disease.

Psychoneuroimmunology is concerned with the complex bidirectional interactions between the CNS (mediating both psychic and biologic processes) and the immune system (not only responsible for resistance to infectious diseases and cancer but also serving newly recognized bioregulatory functions). A ponderous term, psychoneuroimmunology (more accurately, psychoneuroendocrinoimmunology) has also been termed neuroimmunomodulation (thus subsuming psychic influences under neural), behavioral immunology (neglecting the mediation of nervous system), behavioral neuroimmunology, and—perhaps best—psychosocial neuroimmunology. The field reinforces the view that *all* disease is multifactoral and biopsychosocial in onset and course—the result of interrelationships among specific etiologic (e.g., bacteria, viruses, carcinogens), genetic, endocrine, nervous, immune, emotional, and behavioral factors. Psychoneuroimmunology can be subdivided into several aspects. Psychoimmunology deals with the ef-

Received March 9, 1987; revised April 15, 1987; accepted April 16, 1987.

Address reprint requests to Dr. George Freeman Solomon, VA Medical Center, 16111 Plummer Street, Sepulveda, CA 91343.

© 1987 Alan R. Liss, Inc.

fects of personality, stress, emotions, and coping on immunologically resisted diseases (infectious and neoplastic) and on immunologically mediated diseases—those associated with aberration of immune function (allergic and autoimmune) as well as with experimental effects on immunity per se. Immunopsychiatry deals with immunologic abnormalities found in conjunction with mental illnesses and probably also should include psychiatric illness occurring in conjunction with immunologic diseases (such as the psychosis of systemic lupus erythematosus). Immunoneurology deals with the effects of immune factors on the nervous system (such as the role of autoantibodies in multiple sclerosis). Neuroimmunoregulation deals with the control and modulation of immune function by the central and autonomic nervous systems and the neuroendocrines, neurotransmitters, and neuropeptides they produce or control.

In a book chapter of the same title as the 1964 paper (without the "speculative" subtitle) but published 19 yr later, Solomon and Amkraut [14] listed ten "hypotheses" for which evidence should be able to be found "if the central nervous system influences immunologic function." In 1985, in an article by Solomon, 14 hypotheses were listed [15] since by then there were some data to support each. This paper will list 31 (including those 14), reflecting the exponential growth of evidence for bidirectional nervous-immune interactions. The word "postulate" seems more appropriate, in view of its definition as "a hypothesis advanced as an essential pre-supposition, condition, or premise of a train of reasoning" (in this case, immune-neuronal interaction). Evidence for each postulate varies from very substantial to merely suggestive. It would be far beyond the scope of this brief, theoretical overview to cite all evidence for (or against) each postulate; therefore, I shall only cite some illustrative or suggestive supporting evidence for each. Postulates are not listed in any "logical" sequence but as developed, reflecting historical development of the field. The resultant intermingling of psychological, psychiatric, and biophysiological constructs may serve to emphasize the inextricability of "psycho" from "neuro."

I. Enduring coping style and personality factors (so-called "trait" characteristics) should influence the susceptibility of an individual's immune system to alteration by exogenous events.

A variety of personality factors have been linked in clinical research to susceptibility to autoimmune diseases, particularly rheumatoid arthritis, and to stress, coping patterns, and emotions to course [15]. Moos and Solomon found that female patients with rheumatoid arthritis show more masochism, self-sacrifice, denial of hostility, compliance-subservience, depression, and sensitivity to anger than their healthy sisters and are described as always having been nervous, tense, worried, highly strung, moody individuals [16,17]. Physically healthy relatives with rheumatoid factor (an IgM anti-IgG autoantibody) in their sera—which may dispose to developing the disease—are psychologically healthier than those lacking this autoantibody, the implication being that a combination of physical predisposition and a breakdown of psychological defenses leads to manifest disease [18]. Personality data similar to those obtained from rheumatoid arthritics have been reported for patients with other autoimmune diseases. The involvement of the central nervous system in autoimmunity is further suggested by the finding that left-handedness, determined by the brain, is associated with increased risk of autoimmune disease [19]. A number of studies of cancer patients found personality traits roughly similar to those in patients with autoimmune diseases [20]. A prominent feature of the "type C" (cancer-prone) pattern is difficulty in expressing feelings [21]. Older studies found comparable traits in patients with infectious diseases, such as tuberculosis [22].

Such findings led me to postulate an "immunosuppression-prone personality pattern," suggesting that some characterological types of individuals with particular coping styles are more susceptible to suppressive influences on the immune system by psychological factors (such as "stress") or physical ones (such as virus infection). This concept is similar to that of "alexithymia," referring to characteristics of individuals who are prone to expression of emotional conflict through physical illness [23]. Such persons are out of touch with, unaware of, and unable to express emotions, particularly negative ones.

Recently, Kobasa's interesting work has suggested that in some "hardy" individuals stress does not increase susceptibility to illness [24]. Such individuals are characterized by a commitment to self, an attitude of vigorousness toward the environment, a sense of personal meaningfulness, and a feeling of being in control of their lives. In effect, the "hardiness" of these individuals appears to protect them against immunological effects of emotional upset and distress.

II. Emotional upset and distress (so-called "state" characteristics) should alter the incidence, severity, and/or course of diseases that are immunologically resisted (infectious and neoplastic) or are associated with aberrant immunologic function (allergies, autoimmune diseases, and AIDS, which is also immunologically resisted).

Work documenting the existence prior to an illness of a high frequency of life change requiring adaptation is now familiar [25]. More specifically, a variety of studies indicate that stress events and/or the breakdown of psychological defenses and adaptations are related to the onset of allergic, autoimmune, infectious, and neoplastic diseases [5,20]. In this context, "distress" or "strain"

would be a more appropriate term than stress, one definition of which is an extraordinary demand on physiological and/or psychological defenses with concomitant neuroendocrine responses. The individual's perception of the event is critical since a stress for one might be exciting fun for another (e.g., a sky dive). Moos and I found that the course of rheumatoid arthritis appears to be related to the integrity of an individual's psychological defenses. Patients with weak psychological defenses and consequent dysphoria are more likely to have rapidly progressing disease, to be more incapacitated, and to respond less well to medical treatment [26–28]. Klopfer had similar findings in a predictive study of patients with metastatic carcinoma [29], as had other researchers in the case of several infectious diseases [30]. New results suggest that length of survival in AIDS can be correlated with psychosocial factors [31].

III. Severe emotional disturbance and mental dysfunction should be accompanied by immunologic abnormalities.

A variety of immunologic abnormalities, some of which are confusing and contradictory, have been reported in conjunction with mental illness, particularly schizophrenia [4]. Immune abnormalities found in conjunction with schizophrenia may well be epiphenomena not intrinsically related to the disease but reflecting disturbed immunoregulation. Immunologic abnormalities reported in schizophrenics include quantitative and (less convincingly) qualitative alterations in immunoglobulin levels, weakened immune response to administered antigens, and increased incidence of a variety of autoantibodies [4]. Profound perturbation of function in one linked system should be reflected in the other. The suggestion of agonist-behaving autoantibodies to dopamine receptor sites in intriguing [32]. A consistent finding has been the presence in some schizophrenic patients of morphologically and, in some studies, functionally abnormal lymphocytes [33]. These cells have some features of activated T-cells, similar to those found in autoimmune diseases [34]. Might the brain atrophy found in some, but not all, schizophrenic patients [35] be a *secondary* phenomenon in those schizophrenics who happen to develop autoimmune antibrain activity as a result of immune dysregulation?

IV. Diseases of immunologic aberration should, at times, be accompanied by psychological and/or neurological symptoms.

The most obvious evidence for this contention is the psychosis associated with the autoimmune disease systemic lupus erythematosus, which can be very similar symptomatically to schizophrenia. This psychiatric disorder can even be a presenting symptom of the disease, which improves when the underlying physiological disorder is treated [36].

V. Experimental behavioral manipulation—for example, stress, conditioning, and early experience—should have immunologic consequences.

This postulate has already been illustrated [8–10].

VI. Experimental manipulation of appropriate parts of the CNS should have immunologic consequences.

This postulate has been illustrated [12,13]. Additionally, interesting recent French work implicates the cerebral cortex in immunoregulation in a laterally differential way. In mice an intact left cerebral cortex is necessary for the production of T-cell-inducing factors [37]. The cortex does not affect B-cell activity. Portions of the immune system itself are significantly infiltrated with nerve endings. The thymus has nerve-end fibers from the vagus, which originates in the brainstem, and from other sources [38]. The bone marrow, a source of B-cells, also has a good nerve supply [39], and brain lesions affect marrow functions [40]. The sympathetic nervous system is involved in immunoregulation [41].

VII. Activation of the immune system (for example, through immunization) should be accompanied by altered phenomena in the CNS.

In animals that respond to an immunizing antigen, the firing rates of neurons (as determined by implanted electrodes) increase in the ventromedial nuclei of the hypothalamus [42].

VIII. Substances regulated by the CNS (neuroendocrines) or elaborated by the CNS (neurotransmitters and neuropeptides) should influence immune mechanisms.

The effect of hormones on immune response has been the subject of many reviews [43]. Stress-affected hormones including those from the adrenal gland, pituitary (particularly growth hormone), pancreas (insulin), and thyroid all influence the immune response. Neurotransmitters are involved. For example, serotonin delays primary immune responses and lowers intensity of primary and secondary antibody response [44]. A rapidly increasing body of work suggests that the most critical mediators of CNS-immune transactions are the neuropeptides, which Morley et al recently referred to as "conductors of the immune orchestra" [45]. This topic is very complex. For example, while β-endorphin and met-enkephalin enhance NK cell activity in vitro [46], naloxone blocks suppressive effects on NK cell activity by the sort of stress that induces opiate-mediated analgesia [47]. Stress-related neuropeptides and neurohormones significantly modulate the capacity of macrophages to attain a tumoricidal state, suggesting that alteration of macrophage function by neuropeptides may relate to stress-induced enhancement of neoplastic disease [48].

IX. Immunologically competent cells should have receptor sites for neuroendocrines, neurotransmitters, and neuropeptides and for substances regulated by them.

A number of investigators continue to find receptors on lymphocytes or thymocytes for hormones controlled by the CNS, including corticosteroids, insulin, testosterone, estrogens, β-adrenergic agents, histamine, growth hormone, acetylcholine, and met-enkephalin. Presumably, the presence of a receptor site implies a function for its substrate. Some substrates have been identified as playing a role in stimulating the differentiation of lymphocytes and in controlling their activity [49].

X. Feedback mechanisms in immune regulation should act, at least in part, via mediation of the central nervous system.

Serum levels of adrenal cortical steroid hormones are elevated in response to an antigen or graft rejection, presumably via the influence of ACTH, which is controlled by the hypothalamus [50]. This finding suggests a feedback loop between the immune system and the hypothalamic-endocrine system. Antigen stimulates immune response, which leads to a rise in cortisol, which, in turn, tends to suppress the immune response. Such an endocrine response has been postulated as an explanation for the phenomenon of antigenic competition, in which the response to one antigen inhibits the response to another [51]. Another feedback mechanism is suggested by the finding that T-cells not produced in response to an antigen are more sensitive to the inhibitory effects of steroids than T-cells that are so responding. This phenomenon points to a modulating feedback loop that prevents such sensitized T-cells from being overstimulated by the immunohormones (lymphokines) that are released after antigenic stimulation and that increase the activities of a variety of cells involved in immune responses. A decreased noradrenaline turnover in the hypothalami of rats occurs at the peak of immune response [52]. This effect was duplicated by injecting into rats lymphokines released by immunologic cells in vitro. Thus, it appears that lymphokines, a product of the immune reaction, may induce autonomic and endocrine mechanisms that, controlled by the central nervous system, contribute to immunoregulation. The production and action of immunoregulatory cytokines, including interleukin-1 (IL-1), are inhibited by glucocorticoid hormones. Conversely, IL-1 increases glucocorticoid levels via pituitary-adrenal stimulation—an immunoregulatory feedback circuit [53].

XI. Factors elaborated by the immune system should affect the central nervous system and substances regulated by it.

Infused radioactive thymosin α, known to influence maturation of T-cells, can be found in circumventricular areas of the brain involving neuroendocrine regulation [54]. Lymphocytes themselves are a source of γ-endorphin and ACTH [55]. Activated T-helper cells produce the peptide neurotransmitter met-enkephalin [56]. Anti-brain antibodies are claimed, in Yugoslav work, to affect both conditioned learning and the immune response, and Russians claim that thymic hormones (important in T-cell function as well as T-cell maturation) influence learning [57]. Animals from which the thymus has been removed showed delayed sexual maturation, presumably through neuroendocrine mediation [58].

XII. Biochemical and functional similarities might be expected between substances modulating the function and reactivity of the CNS (neuropeptides) and substances with comparable effects on the immune system (lymphokines).

An ever-increasing number of low molecular weight proteins (polypeptides) are being identified as modulating the sensitivity of the CNS. These compounds have slower and more prolonged actions than neurotransmitters. Likewise, a considerable number of peptides that are products of immunologically competent cells—the lymphokines—have been identified as amplifying, activating, and controlling immune response. (An analogy has been made between a synapse and the junction between a macrophage and a lymphocyte. E.M. Smith, personal communication, 1984.) Similarities between the two systems are also suggested by the fact that a variety of substances affect both. It was just noted in postulate XI that the thymic hormones (among them, thymosin α) seem to affect the CNS as well as the immune system. Enkephalin and endorphin affect both systems. ACTH stimulates corticosteroid and β-endorphin production. Both enkephalin and ACTH are part of the same precursor molecule. There are also antigenic and structural similarities among ACTH, β-endorphin, and human leukocyte interferon [55]. Apparently there are even some similarities in the structure of specific proteins of the thymus and the cerebral cortex [59].

XIII. Thymic hormones regulating immune function should be influenced by the CNS.

There is growing evidence of bidirectional interactions between the thymus and the neuroendocrine system. Thymosin β elicits the release of luteinizing-hormone-releasing factor, and injecting thymosin β intraventricularly increases the serum levels of luteinizing hormone [60]. Neuroendocrines influence the production of thymic hormones [61]. Lethargic mice, a mutant strain, suffer from a neurologic abnormality that develops before weaning, lasts 30–60 d, and then gradually disappears. This neurological disease is associated with thymic atrophy; the thymus returns to normal as soon as the neural disturbance disappears [62]. Both thymectomized and nude mice, another mutant strain that shows thymic atrophy, display a profoundly disturbed neuroendocrine balance [63]. There is a report of the extraction from the anterior pituitary of a low molecular weight peptide with thymocyte-stimulating properties [64]. Oxytocin and

neurophyspin, neurohypophyseal peptides, have been identified in the human thymus, supporting a neuroendocrine function for the thymus [65].

XIV. Behavioral interventions (such as psychotherapy, relaxation techniques, imagery, biofeedback, and hypnosis) should be able to enhance or optrimize immune function.

If "noxious affects" (such emotions as anxiety, grief, depression, and loneliness) are immunosuppressive, then it stands to reason that whatever psychotherapeutic or psychopharmacologic intervention makes for a distress-free state of mind might be expected to improve immune function. Recovery from a major depressive illness is accompanied by reversal of depression-associated immunosuppression [66]. An important question is whether behavioral intervention can enhance immunity. Psychoneuroimmunologic research on the effects of such interventions on specific aspects of the immune response is just beginning. Are the innumerable reports of successful behavioral interventions (from psychoanalysis to faith healing and to visualizing "good" white blood cells eating up "bad" cancer cells) in a variety of physical diseases, particularly cancer and the autoimmune diseases, the result, at least in some cases, of psychoneuroendocrine effects on immune function? One unique study found that young, highly hypnotizable subjects were able to increase the in vitro proliferative response of their lymphocytes to pokewood mitogen (which stimulates both B- and T-cells) when given the suggestion under trance that their white blood cells were like "powerful sharks" destroying "weak germs" [67]. (Many studies have noted that hypnosis can moderate such inflammatory responses as histamine-induced wheals.) Henry and Meehan conceptualize behavior as a continuum from effort to relaxation and mood as a continuum from euphoria to distress, and at different points of a continuum they identify responses along the pituitary-adrenal cortical axis and the sympathetic-adrenal medullary axis [68]. Are happiness, security, sense of control, relaxation, and other positive emotions accompanied by immune enhancement? The work remains to be done, work certainly likely to be of relevance to clinical medicine.

XV. Altered CNS neurotransmitter receptor site sensitivities felt to be associated with mental illnesses should be reflected in lymphocyte receptors.

Patients with endogenous depression associated with psychomotor agitation show reduced sensitivity of lymphocyte β-adrenergic receptors [69]. Depressed patients have lower basal lymphocyte cytoplasmic glucocorticoid receptor content than controls [70].

XVI. Neurotropic virus should also show affinity for lymphocytes and vice versa.

Human immunodeficiency virus (HIV, formerly known as HTLV-III, the AIDS-associated virus, which attacks helper/induced T-cells, also attacks the CNS and can produce organic brain syndromes in patients with AIDS and ARC (AIDS-related complex) [71]. Not only brain macrophages but also microglia and astrocytes and probably neurons appear to be infected, but direct entry of virus into neural cells is controversial [72]. The T4 receptor found in helper/inducer T-cells is also found in brain, probably located on neurons. Evidence is growing that HIV may not only infect brain cells but may interfere with a normally occurring substances in the brain, just as it may interfere with the IL-2 receptor on lymphocytes [73]. Symptomatic infection of the CNS by HIV can occur without evidence of immune deficiency [74]. Measles virus RNA is found both in brain (perivascular infiltrates and neurons) and in lymphocytes in patients with subacute sclerosing panencephalities [75].

XVII. The "functional" modes of expression of CNS and immune system should be similar.

Based on the complex, now-being-unravelled nature of antibody, anti-idiotype antibody (antibodies against the variable region of antibodies) formation, Neils Jerne suggested in his 1984 Nobel lecture that there is a basic analogy between linguistics and immunology. There is, thus, an inheritable capacity to learn language in both CNS and immune system. The immune response is a "sentence" with its own grammer, not a "word" [76].

XVIII. At least some psychotropic drugs should have receptor sites on and functionally affect immunologically competent cells.

Benzodiazepines, widely utilized for antianxiety effects, are potent stimulators of human monocyte chemotaxis, likely mediated by the peripheral-type benzodiazepine receptor [77]. Tricyclic antidepressants have binding sites on splenic lymphocytes and suppress mitogen response [78].

XIX. Some cell types should be common to both immune and neuro-endocrine systems.

Cells containing chromogranin, a secretory protein marker for the neuroendocrine system, are found in spleen, lymph nodes, thymus, and fetal liver. These cells may be significant in neuroimmunomodulatory interactions [79].

XX. Immunomodulators should alter opiate-related CNS-mediated physiological and behavioral responses.

Both α-interferon and the immunosuppressant drug cyclosporine modify symptoms of naloxone-induced abstinence syndrome in morphine-addicted rats [80,81].

XXI. There should be biochemical similarities (with functional implications) between cell surface constituents of neurons and of immunologic cells.

The Thy-1 glycoproteins are major cell surface constituents of rodent thymocytes and neurons [82]. Antibodies to Thy-1 can stimulate T-lymphocytes to release lymphokines and undergo cell division.

XXII. An "immuno-pituitary-adrenal axis" may exist parallel to the hypothalamo-pituitary-adrenal axis.

Monocytes can release hepatocyte-stimulatory factor and interleukin-1, both of which can induce pituitary cells to release ACTH [83]. ACTH can regulate lymphokine production [84].

XXIII. Specificity characterizes both immunologic and olfactory (CNS-based) systems, and links between these specificities may have to do with the emotionally and immunologically related disease, bronchial asthma [85].

XXIV. Prenatal hormonal environment may affect both CNS development with behavioral consequences and immune development with long-lasting alterations in the components and function of the immune system.

Women exposed to diethylstilbestrol (DES) in utero show increased homosexuality and bisexuality [86]. Proportions of T-cell subpopulations, particularly reduction in T-helper cells, and of B-cells are altered in adult mice, the mothers of which were treated with DES during pregnancy. There are long-lasting effects on ability to respond to antigenic stimuli [87].

XXV. Early life experiences, recognized since Freud [88] as critical to adult psychological functioning, should influence adult immune function.

Handling infant rats for 3 min a day from birth until weaning (21 d) enhances primary and secondary antibody response to a novel antigen [9].

XXVI. Sleep should have a role in immunologic as well as CNS function.

Interferon, as well as other lymphokines, can enhance slow-wave sleep, and interferon decreases REM latency, "suggesting that sleep may play an important role in recuperative process whether it is recovery from a day's activity or from damage induced by a disease" [89,90]. Interleukin-1 increases in conjunction with onset of slow-wave sleep [91]. (Does disturbance of sleep, as occurs in conjunction with depression and with stress, contribute to the associated impairment of immunity?)

XXVII. Substances with neurotropic activity may also function as lymphocyte growth factors.

"Neuroleukin" promotes survival of spinal and sensory neurons (not autonomic) and is also a lymphokine product of stimulated T-cells that appears to induce polyclonal B-cell maturation to immunoglobulin secretion (monocyte- and T-cell-dependent) [92,93].

XXVIII. Surface receptors for nonantigen, non-major-histocompatibility complex (MHC) glycoproteins thought to play accessory roles in processes of recognition and signal transduction might be expected to appear both on lymphocytes and neural tissues. L3T4 is expressed on helper/inducer T-cells and also is found in brain [94].

XXIX. Longevity should be correlated with superior immune function as well as with superior psychological status (e.g., coping, "hardiness," interpersonal relationships).

Beta-endorphin stimulation of NK cells of significant degree occurs in 43% of healthy elderly subjects (over 65) but only 21% of young controls (20–40) and is significant correlated with emotional "hardiness" in the elderly [95]. In a 40-yr longitudinal study of Harvard sophomores, psychological health predicted physical health [96]. Coping with stress was of particular relevance to morbidity and premature mortality.

XXX. CNS-active substances administered intraventricularly should produce effects on immune functions—effects that the same substances do not produce when administered systemically or when exposed to immunologically competent cells in vitro.

Work in this area is currently underway in some laboratories and is highly suggestive of receptor-mediated phenomena in the brain affecting immunity. (Such phenomena may be responsible for alterations in immune function associated with psychiatric conditions.)

XXXI. Naturally occurring life stresses should be associated with immunosuppression.

The stress of "examination week" activates latent herpes simplex virus infection (under T-cell control) in medical students—to a greater degree in lonely students [97]. Family caregivers of victims of Alzheimer's disease have reduced helper/suppressor T-cell ratios and lower immune control of latent Epstein-Barr virus [98]. Poor marital quality and recent separation or divorce are associated with reduction in several qualitative and quantitative measures of immune function—both correlated, in turn, with degree of consequent depression [99].

CONCLUSION

The reader may well, even at this point in time, be able to add more "postulates" or "hypotheses." To borrow forensic terms, the "preponderance of evidence" links the nervous (both central and "autonomic") and immune systems "beyond a reasonable doubt." The exponential growth of the field of psychoneuroimmunology and consequent accretion of experimental evidence will, no doubt, make many of the implications herein advanced seem more convincing, may render others incorrect, and will provide evidence for new implications. It was deliberate to use the word "field" in the singular, as a trans- or interdisciplinary integration, acknowledging the multifactoral nature of *all* disease as the result of interactions among genetic, endocrine, nervous, immune, and behavioral-emotional factors. Such a frame of reference has been championed by such pioneers as George Engel [100]

and Jonas Salk [101] and has also been sensed by wise clinicians since ancient times—from practitioners of Ayurveda in India of two millenia ago [101] to Hippocrates, Galen, and Osler.

REFERENCES

1. Ader R (ed) (1981) "Psychoneuroimmunology." New York: Academic Press.
2. Solomon GF, Moos RH (1964): Emotions, immunity, and disease. A speculative theoretical integration. Arch Gen Psychiatry 11:657–674.
3. Solomon GF, Moos RH, Fessel WJ, Morgan EE (1966): Globulins and behavior in schizophrenia. Int J Neuropsychiatry 2:20–26.
4. Solomon GF (1981): Immunologic abnormalities in mental illness. In Ader R (ed): "Psychoneuroimmunology." New York: Academic Press, pp 259–278.
5. Solomon GF (1981): Emotional and personality factors in the onset and course of autoimmune disease, particularly rheumatoid arthritis. In Ader R (ed): "Psychoneuroimmunology." New York: Academic Press, pp 159–179.
6. Dixon FJ, Feldman J, Vasquez J (1961): Experimental glomerulonephritis. J Exp Med 113:899.
7. Hamburg DA (1962): Plasma and urinary corticosteroid levels in naturally occurring psychological stresses. Res Publ Assoc Res Nerv Ment Dis 40:406.
8. Solomon GF (1969): Stress and antibody response in rats. Int Arch Allergy 35:97–104.
9. Solomon GF, Levine S, Kraft JK (1968): Early experience and immunity. Nature 220:821–822.
10. Ader R, Cohen N (1975): Behaviorally conditioned immunosuppression. Psychosom Med 37:333–340.
11. Metal'nikov S, Chorine V (1926): The role of conditioned reflexes in immunity. Ann Pasteur Inst 40:893–900.
12. Korneva EA, Khai LM (1963): Effects of destruction of hypothalamic areas on immunogenesis. Fiziol Zh SSSR 49:42.
13. Korneva EA (1967): The effects of stimulating different mesencephalic structures on protective immune response pattern. Fiziol Zh SSSR 53:42–45.
14. Solomon GF, Amkraut AA (1983): Emotions, immunity and disease. In Temoshok L, Van Dyke C, Zegans LS (eds): "Emotions in Health and Illness: Theoretical and Research Foundations." Ne York: Grune and Stratton, pp 167–186.
15. Solomon GF (1985): The emerging field of psychoneuroimmunology with a special note on AIDS. Adv 2:6–19.
16. Moos RH, Solomon GF (1965): Psychologic comparisons between women with rheumatoid arthritis and their non-arthritic sisters. I. Personality test and interview rating data. Psychosom Med 27:135–149.
17. Moos RH, Solomon GF (1965): Psychologic comparisons between women with rheumatoid arthritis and their non-arthritic sisters. II. Content analysis of interviews. Psychosom Med 27:150–164.
18. Solomon GF, Moos RH (1965): The relationship of personality to the presence of rheumatoid factor in asymptomatic relatives of patients with rheumatoid arthritis. Psychosom Med 27:350–360.
19. Marx JL (1982): Autoimmunity in left-handers. Science 217:141–144.
20. Bahnson CB (1980, 1981): Stress and cancer, state of the art, Part I. Psychosomatics 21:975–981. 1980. Part 2. Psychosomatics 22:207–220, 1981.
21. Levy, SM (1983): The expression of affect and its biological correlates: Mediating mechanisms of behavior and disease. In Temoshok L, Van Dyke C, Zegans LS (eds): "Emotions in Health and Illness. Applications to Clinical Practice." New York: Grune & Stratton, pp 1–18.
22. Sparer PJ (ed) (1956): "Personality, Stress and Tuberculosis." New York: International Universities Press.
23. Nemiah JC, Sifneos PE (1970): Affect and fantasy in patients with psychosomatic disorders. In Hill OW (ed) "Modern Trends in Psychosomatic Medicine." New York: Appleton-Century-Crofts, pp 26–31.
24. Kobasa SC (1979): Stressful life events, personality and health: An inquiry into hardiness. J Pers Soc Psychol 37:1–11.
25. Rahe RH, Arthur RJ (1978): Life change and illness studies: Past history and future directions. J Human Stress 4:3–15.
26. Moos RHV, Solomon GF (1964): Personality correlates of the rapidity of progression of rheumatoid arthritis. Ann Rheum Dis 23:145–151.
27. Moos RH, Solomon GF (1965): Personality correlates of the degree of functional incapacity of patients with physical disease. J Chronic Dis 18:1019–1038.
28. Solomon GF, Moos RH (1965): Psychologic aspects of response to treatment in rheumatoid arthritis. GP 32:113–119.
29. Klopfer B (1957): Psychological variables in human cancer. J Proj Tech 21:331–340.
30. Meyer RJ, Haggerty RJ (1962): Streptococcal infection in families. Factors altering individual susceptibility. J Pediatr 29:539–549.
31. Temoshok L, Zich J, Solomon GF, Stites D: An intensive psychoimmunologic study of long-surviving persons with AIDS: III International Conference on AIDS, Washington, June 1, 1987.
32. Knight JG (1982): Dopamine-receptor stimulating auto-antibodies: A possible cause of schizophrenia. Lancet 82:1073–1076.
33. Fessel WJ, Hirata-Hibi M (1963): Abnormal leukocytes in schizophrenia. Arch Gen Psychiatry 9:601–613.
34. Higashi S, Hirata-Hibi M, Tachibana T, Watanabe N (1982): Stimulated lymphocytes in schizophrenia. Arch Gen Psychiatry 39:82–87.
35. Losonczy MF, Song IS, Mohs RL, Mathe AA, Davidson M, Davis BM, Davis KL (1986): Correlates of lateral ventricular size in chronic schizophrenia. II: Biological measures. Am J Psychiatry 143:1113–1117.
36. Fessel WJ, Solomon GF (1960): Psychosis and systemic lupus erythematosus: A review of the literature and case reports. Calif Med 92:266–270.
37. Renoux G, Biziere K, Renoux M, Guillamin JM (1983): The production of T-cell inducing factors in mice is controlled by the brain neocortex. Scand J Immunol 145–150.
38. Bulloch K, Moore RY (1981): Innervation of the thymus gland by brain stem and spinal cord in mouse and rat. Am J Anat 162:157–166.
39. Calvo W (1968): The innervation of the bone marrow in laboratory animals. Am J Anat 123:315.
40. Baciu I (1962): La regulation nerveuse et humorale di l'erythropoiese. J Physiol (Paris) 54:441.
41. Besedovsky HO, Del Rey A, Sorkin E, Da Prada M, Keller HH (1979): Immunoregulation mediated by the sympathetic nervous system. Cell Immunol 48:346.
42. Klimenko VM (1985): Neural hypothalamic mechanisms in the development of the immune response. In Korneva EA, Klimenko VM, Shkhinek EK (eds): "Neurohumoral Maintenance of Immune Homeostasis." Chicago: Univ. Chicago Press, pp 159–167.
43. Mac Lean D, Reichlin S (1981): Neuroendocrinology and the immune process. In Ader R (ed): "Psychoneuroimmunology."

New York: Academic Press, pp 475–520.
44. Devoino LV, Idova GV (1973): The influence of some drugs on the immune response IV. Effect of serotonin, 5-hydroxytryptophan, iproniazid, and p-chorophenylalanine on the synthesis of IgM and IgG antibodies. Eur J Pharmacol 22:325–331.
45. Morley JE, Kay NE, Solomon GF, Plotnikoff NP Neuropeptides: Conductors of the immune orchestra. Life Sciences (in press).
46. Mathews PM, Froelich CJ, Sibbit WL, Bankhurst AD (1983): Enhancement of natural cytotoxity by β-endorphin. J Immunol 130:1658–1662.
47. Shavit Y, Lewis JW, Terman GW, Gale RP, Liebeskind JC (1984): Opioid peptides mediate the suppressive effects of stress on natural killer cell cytotoxicity. Science 223:188–190.
48. Koff WC, Dunegan MA (1985): Modulation of macrophage-mediated tumoricidal activity by neuropeptides and neurohormones. J Immunol 135:350–354.
49. Helderman JH, Strom TB (1978): Specific binding site on T and B lymphocytes as a marker of cell activation. Nature 274:62–63.
50. Besedovsky HO, Sorkin E, Keller HH (1978): Changes in the concentration of corticosterone in the blood during skin graft rejection in the rat. J Endocrinol 76:175–176.
51. Hall NR, Goldstein AL (1983): Role of thymosin and the neuroendocrine system in the regulation of immunity. In Fabris N, Garaci E, Hadden J, Mitchison NA (eds): "Immunoregulation." New York: Plenum, pp 141–163.
52. Besedovsky HO, Del Rey A, Sorkin E, Da Prada M (1983): The immune response evokes changes in brain noradrenergic neurons. Science 221:564–565.
53. Besedovsky HO, del Rey A, Sorkin E, Dinarello CA (1986): Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. Science 233:652–654.
54. Hall NR, Goldstein AL (1983): The thymus-brain connection: Interactions between thymosin and the neuroendocrine system. Lymphokine Res 2:1–6.
55. Smith EM, Blalock JE (1981): Human lymphocyte production of corticotropin and endorphin-like substances: Association with leukocyte interferon. Proc Natl Acad Sci USA 78:7530–7534.
56. Zurawaki G, Benedik M, Kamb BJ, Abrams JS, Zurawski SM, Lee FD (1986): Activation of mouse T-helper cells induces abundant preproenkephalin mRNA synthesis. Science 232:772–775.
57. Jancović BD (1984): Immunomodulation of neural structures and functions. Paper delivered at Soviet Academy of Sciences conference, "Regulation of Immune Homeostasis," Leningrad, 1982. Published in USSR in 1984.
58. Besedovsky HO, Sorkin E (1974): Thymic involvement in female sexual maturation. Nature 249:356–358.
59. Valueva TK, Malyzchev VA (1984): The role of various humoral thymic factors in antigen-independent T-lymphocyte differentiation. Paper delivered at Soviet Academy of Sciences conference, "Regulation of Immune Homeostatis," Leningrad, 1982. Published in USSR.
60. Rebar RW, Miyake A, Low TLK, Goldstein AL (1981): Thymosin stimulates secretion of luteinizing hormone-releasing factor. Science 213:669–671.
61. Fabris N (1984): Endocrine control of thymic factor production in young adult and old mice. Paper prepared for Soviet Academy of Sciences conference, "Regulation of Immune Homeostasis," Leningrad, 1982. Published in USSR.
62. Dung HC (1977): Deficiency in the thymus-dependent immunity in "lethargic" mutant mice. Transplantation 23:39.
63. Fabris N, Mocchegianni E, Muzzioli M, Imberti R (1983): Thymusneuroendocrine network. In Fabrris N, Garaci E, Hadden J, Mitchison NA (eds): "Immunoregulation." New York: Plenum Press.
64. Saxena RK, Talwar GP (1977): An anterior pituitary factor stimulated thymidine incorporation in isolated thymocytes. Nature 268:57.
65. Geenen R, Legros J-J, Franchimont P, Baudrihaye NM, Defresne M-P, Boniver J (1986): The neuroendocrine thymus: Coexistence of oxytocin and neurophysin in the human thymus. Science 232:508–511.
66. Stein M, Keller SE, Schleifer SJ (1985): Stress and immunomodulation; the role of depression and neuroendocrine function. J Immunol 135:827–833.
67. Hall HH (1983): Hypnosis and the immune system: A review with implications for cancer and the psychology of healing. Am J Clin Hypnosis 25:92–103.
68. Henry JP, Meehan JP (1981): Psychosocial stimuli, physiological specificity and cardiovascular disease. In Weiner H, Hofer MA, Stunkard AJ (eds): "Brain, Behavior and Bodily Disease." New York: Raven Press, pp 305–333.
69. Mann JJ, Brown RP, Halper JP, Sweeney JA, Kocsis JH, Stokes PA, Bilezian FP (1985): Reduced sensitivity of lymphocyte beta-adrenergic receptors in patients with endogenous depression and psychomotor agitation. N Engl J Med 313:715–720.
70. Gormley GJ, Lowry MT, Reder AL, Hospelhorn VD, Antel JP, Meltzer HY (1985): Glucocorticoid receptors in depression: Relationship to the dexamethasone suppression test. Am J Psychiatry 142:1278–1284.
71. Shaw GM, Harper ME, Hahn BH, et al (1985): HTLV-III infection in brain of children and adults with AIDS encephalopathy. Science 227:177–182.
72. Barnes DM (1987): Brain damage by AIDS under active study. Science 235:1574–1577.
73. Weigent DA, Hoeprich PD, Bost KL, Brunck TK, Reiher WE, Blalock JE (1986): The HTLV-III envelope protein contains a hexapeptide homologous to a region of interleukin-2 that binds to the interleukin-2 receptor. Biochem Biophys Res Commun 139:367–374.
74. Beckett A, Summergrad P, Manschreck T, et al Symptomatic HTLV-III infection of the central nervous system in a patient without clinical evidence of immune deficiency. Am J Psychiatry (in press).
75. Fournier JG, Tardieu M, Lebon P, Robain O, Ponsot G, Rozenblatt S, Bouteille M (1985): Detection of measles virus RNA in lymphocytes from peripheral blood and brain perivascular infiltrates of patients with subacute sclerosing panencephalitis. N Engl J Med 313:910–915.
76. Jerne NK (1985): The generative grammer of the immune system. Science 229:1057–1059.
77. Ruff MR, Pert CB, Weber RJ, Wahl SM, Paul SM (1985): Benzodiazepine receptor-mediated chemotaxis of human monocytes. Science 229:1281–1283.
78. Audus KL, Gordon MA (1985): Tricyclic antidepressant effects on the murine lymphocyte mitogen response. Immunopharmacology 4:13–27.
79. Angeletti RH, Hickey WF (1985): A neuroendocrine marker in tissues of the immune system. Science 230:89–90.
80. Dafny N, Reyes-Vasquez C (1985): Three different types of alpha-interferons alter nalozone-induced abstinence in morphine-addicted rats. Immunopharmacology 9:13–17.
81. Dafny N, Wagle VS, Drath DB (1985): Cyclosporine alters opiate withdrawal in rodents. Life Sci 36:1721–1726.
82. Tse ASD, Barclay N, Watts A, Williams AF (1985): A glycophospholipid tail at the carboxyl terminus of the Thy-1 glycoprotein of neurons and thymocytes. Science 230:1003–1008.
83. Woloski MRNJ, Smith EM, Meyer WJ III, Fuller SM, Blalock

JE (1985): Corticotropin-releasing activity of monokines. Science 230:1035–1036.
84. Johnson HM, Torres BA, Smith EN, Dion LD, Blalock JE (1984): Regulation of lymphokine (interferon) production by corticotropin. J Immunol 132:246–259.
85. Stein M (1986): A reconsideration of specificity in psychosomatic medicine: From olfaction to the lymphocyte. Psychosom Med 48:3–22.
86. Ehrhardt AA, Mayer-Bahlburg HFL, Rosen LR, et al (1985): Sexual orientation after prenatal exposure to exogenous estrogen. Arch Sex Behav 14:57–75.
87. Blair PB (1981): Immunologic consequences of early exposure of experimental rodents to diethylstilbestrol and steroid hormones. In Herbst AL, Bern HA (eds): "Developmental Effects of Diethylstilbestrol in Pregnancy." New York: Thieme-Stratton, pp 167–178.
88. Freud S (1953): "Three Essays on the Theory of Sexuality (1905)." Standard Edition, Vol. VII. London: Hogarth Press.
89. Reite M, Laudenslager M, Jones J, Crmic L, Kaemingk K Interferon decreases REM latency. Biol Psychiatry (in press).
90. Krueger JM Immune modulators as sleep promotors. Ann NY Acad Sci (in press).
91. Moldofsky H, Lue FA, Eisen J, Keystone E, Gorczynski RM (1986): The relationship of interleukin-1 and immune functions to sleep in humans. Psychosom Med 48:309–318.
92. Gurney ME, Heinrich SP, Lee MR, Yin HS (1986): Molecular cloning and expression of neuroleukin, a neurotrophic factor for spinal and sensory neurons. Science 234:566–574.
93. Gurney ME, Apatoff BR, Spear GT, et al (1986): Neuroleukin: A lymphokine product of lectin-stimulated T cells. Science 234:574–581.
94. Tourvieille B, Gorman SD, Field EH, Hunkapiller T, Parnes T (1986): Isolation and sequence of L3T4 complimentary DNA clones: Expression in T cells and brain. Science 234:610–614.
95. Solomon GF, Fiatarone MA, Benton D, Morley JE, Bloom E, Makinoden T: Psychoimmunologic and endorphin function in the aged. Ann NY Acad Sci (in press).
96. Vaillant GE (1979): Natural history of male psychological health: Effects of mental health on physical health. N Engl J Med 301:1249–1254.
97. Glaser R, Kiecolt-Glaser JK, Speicher CE, Holiday JE (1985): Stress, loneliness, and changes in herpes virus latency. J Behav Med 8:249–260.
98. Kiecolt-Glaser JK, Glaser R, Shuttleworth EC, Dyer CS, Ogrocki P, Speicher CE Chronic stress and immunity in family caregivers of Alzheimer's disease victims. Psychosom Med (in press).
99. Kiecolt-Glaser JK, Fisher LD, Ogrocki P, Stout JS, Speicher CE, Glaser R (1987): Marital quality, marital disruption, and immune function. Psychsom Med 49:13–34.
100. Engel GL (1960): A unified concept of health and disease. Perspect Biol Med 3:459–485.
101. Salk J (1962): Biological basis of disease and behavior. Perspect Biol Med 5:198–206.
102. Shukla HC, Solomon GF, Doshi RP (1979): The relevance of some Ayurvedic (traditional Indian medical) concept to modern holistic health. J Holistic Health 4:125–131.

ADDENDUM

Four additional "postulates" regarding evidence for CNS-immune system similarity and interaction arise from presentations made at the First Stromboli Conference on Aging and Cancer, a NATO Advanced Research Workshop, on the topic "Neuroimmunomodulation: Interventions in Aging and Cancer," held June 7–11, 1987 in Stromboli, Sicily, Italy.

XXXII. Enzymes related to synthesis of neurotransmitters in the brain should be found in immunologically competent cells, especially neurons.

Tetrahydrobiopterin (BH_4) plays an important role in regulating synthesis of dopamine and serotonin in the CNS. BH_4 levels in CSF are decreased in Parkinson's and Alzheimer's diseases. BH_4 is synthesized and contained in lymphocytes. Stimulated macrophages release neopterin. Biopterin excretion in the urine is increased in viral diseases, particularly AIDS. The function of the pterins in the immune system is currently unknown [A].

XXXIII. Melatonin, a neurally regulated hormone related to circadian rhythmicity and affected by stress, should affect immunity.

Melatonin plays a major in vivo immunoregulatory role acting on antigen-activated T-lymphocytes via the endogenous opioid system, generally an up-regulatory role. Melatonin can completely block the immunosuppression induced by restraint stress [B].

XXXIV. Aging of immune and neuroendocrine systems are linked.

Treatment of old animals with thyroxin restores thymic production of thymulin. Transplant of neonatal thymuses into old animals corrects age-associated alterations in levels of thyroxin and insulin [C].

XXXV. Since viruses appear to enter cells through naturally present receptor sites, including for neuropeptides, related peptides that block such receptor sites may prevent entry of virus into cells or viral-induced damage to cells—immune and neural.

"Peptide T_{4-8}", a pentapeptide related to a small portion of human immunodeficiency virus (HIV) envelope and to the CNS-active peptide vasoactive intestinal protein (VIP), may block effects of HIV on the immune system and the CNS and provide an approach to treatment of and immunization against AIDS [D].

ADDENDUM REFERENCES

A. Levine R: Involvement of tetrahydrobiopterin, co-factor for tyrosine and tryptophan hydroxylases, in neuropsychiatry, immunology, and aging. Ann NY Acad Sci (in press).
B. Maestroni GJM, Conti A, Pierpaoli W: Pineal melatonin. Its fundamental immunoregulatory role in aging and cancer. Ann NY Acad Sci (in press).
C. Fabris N: Pathways of neuroendocrine-immune interactions and their impact with aging processes. Ann NY Acad Sci (in press).
D. Pert CB, Ruff MR: Neuropeptides, lymphokines, growth factors, and classical hormones as the biochemicals of emotions. Neuropeptides and viruses in CNS and immune system: implications for treatment and prevention of AIDS. Ann NY Acad Sci (in press).