

In H. Friedman, T.W. Klein & A.L. Friedman (Eds.),
Psychoneuroimmunology, stress and infection, CRC Press, Boca Raton, 1995 (pp. 1-21)

Historical Perspectives on Psychoneuroimmunology

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Psychoneuroimmunology refers, most simply, to the study of the interactions among behavioral, neural and endocrine (or neuroendocrine), and immunological processes of adaptation. Its central premise is that homeostasis is an integrated process involving interactions among the nervous, endocrine and immune “systems.” The term was first used in 1980, in my presidential address to the American Psychosomatic Society.¹ Its most conspicuous use was as the title of an edited volume² which one reviewer referred to prophetically as “The signature volume of a new field of research.” This first volume was an attempt to bring together emerging research suggesting a relationship between the brain and the immune system. Traditionally, however, the immune system has been considered an *autonomous* agency of defense — a system of bodily defenses regulated by cellular interactions that are independent of neural influences. Besides, there were no known connections between the brain and the immune system. To be sure, it was known that hormones or, at least, adrenal hormones could influence immunity; some investigators were aware that brain lesions could influence immune responses; and it was also known or, at least, suspected that emotional states were associated with the development or progression of diseases related to the immune system. Few scientists at that time, however, took such observations too seriously. After all, there were no mechanistic explanations for how such things could happen.

Considering the brief time during which multidisciplinary research has addressed brain-immune system interactions, a great deal of data has accumulated in support of the proposition that homeostatic mechanisms are the product of an integrated system of defenses of which the immune system is one component.³ Autonomic nervous system activity and neuroendocrine outflow via the pituitary can influence immune function, and cytokines and hormones released by an

activated immune system can influence neural and endocrine processes. Regulatory peptides and receptors once confined to the brain are expressed by both the nervous and immune systems and each system is thereby capable of modulating the activities of the other. It is hardly surprising, then, to find that immunologic reactivity can be modified by Pavlovian conditioning — or that the behavioral and emotional states that accompany the perception of and the effort to adapt to events in the real world can influence immune responses. Thus, psychoneuroimmunology successfully challenged the commonly held assumption of an autonomous immune system. One may, therefore, entertain the proposition that changes in immune function mediate the effects of psychosocial factors and stressful life experiences on the susceptibility to and/or the precipitation or progression of some disease processes.

It is not my intent, in this introductory chapter, to review the literature outlining the history of psychoneuroimmunology. I have, instead, taken my charge literally and chosen the more manageable task of presenting here some editorial comments and some historical perspectives on psychoneuroimmunology. These are, of necessity, brief and selected and only cover developments up until about 1980. Very much more could be written about the people and the findings described here because these are rich personal stories. Much more could also be written about what was contemporary and what came before and what came after the 1970s, but this is a chapter — not a book. The research I have chosen to highlight was not necessarily even the first of its kind; in my opinion, however, the systematic research initiated during the 1970s was “the right stuff at the right time.” No one study can be said to have been (or could have been) responsible for psychoneuroimmunology. I suspect that none of the research initiatives described below would have had quite the same impact had it not been for the converging evidence of brain-immune system interactions being provided by the others at

about the same time. Studies of brain-immune system relationships had been appearing in the literature for many, many years. However, it was the coalescence of research initiated during the 1970s and sustained thereafter — and the identity provided by the label, psychoneuroimmunology, itself — that reawakened long-standing interests and attracted new investigators into this “new” field.

The notion of integration is neither new nor, for the most part, can it be considered controversial. It was David Hamburg, I think, who pointed out that biochemistry, a hybrid discipline, was initially viewed as a combination of poor biology and weak chemistry. Today, it is basic and central to the study of medicine. Psychopharmacology is a recognition of the fact that drug effects depend to a large extent on the state of the organism into whom they are introduced. Neuroendocrinology reflects an appreciation of the fact that the functions of the endocrine system can not be fully understood without reference to its interactions with the nervous system. And psychoneuroendocrinology acknowledges that the feedback and feedforward pathways between these “systems” influence and are influenced by behavior. Hybrid disciplines are not always or solely attempts at integration or synthesis. Basic fields such as neurochemistry or immunopharmacology, and clinical subspecialties such as neuropsychiatry, for example, designate a focus within a parent “discipline.” In fact, in keeping with the zeitgeist of the biomedical model, the latter reductionistic referent is probably the more common one.

Among other shortcomings, disciplinary boundaries tend to keep insiders in and outsiders out. Hybrid disciplines have nevertheless emerged and significantly extended our understanding of the functions of the components of interacting systems. Why is it, then, that psychoneuroimmunology precipitated — and, in some circles, continues to engender — so much resistance and enmity? Certainly, the attention that psychoneuroimmunology has captured in the popular press and

its exploitation by those who redefine and use psychoneuroimmunology as the scientific umbrella for their own undisciplined and untested theories and practices cannot have endeared psychoneuroimmunology or investigators who study brain-immune system interactions to the remainder of the scientific community. In my unsubstantiated view, however, the reasons lie as much within as without the biomedical community. Some scientists are willing to say they “don’t believe” there’s anything of substance in psychoneuroimmunology, although they are not necessarily willing to be quoted. Of course, scientists do not have recourse to “I don’t believe it” as grounds for rejecting hypotheses. One can argue, “I don’t believe it because...” as in: “I don’t believe it because there are no connections between the brain and the immune system.” Such arguments are capable of disproof and, with respect to psychoneuroimmunology, all such arguments have been contradicted by experimental data. Unfortunately for the development of the field, however, there are those in influential positions who, purportedly, *believed* that psychoneuroimmunology would go nowhere and acted in a consultative capacity on this “belief.” There is, too, a sense of unease among some so-called “hard” scientists who seem to view the scientific study of behavior as an oxymoron. In truth, the sophistication in experimental design and analysis of research by the behavioral sciences far exceeds that of the more classical biomedical sciences and even molecular biology, and is essential for addressing the quantitative questions (e.g., when, how much, under what conditions) that are raised by factoring behavioral, neural and endocrine variables into the experimental analysis of immunoregulatory processes.

Within the field, there have been some minor battles over “turf,” but none has altered the defining theme of the field. The emergence of psychoneuroimmunology has actually broadened some fields of study that were more narrowly defined in the recent past (e.g., papers in psychoneuroimmunology

are now solicited for publication in the *Journal of Neuroimmunology*). “Neuroimmunomodulation” and “neuroendocrinimmunology,” mere mispronunciations of psychoneuroimmunology, seem to have been precipitated to disengage from the study of behavior and/or to more specifically brand the field with one’s own personal or disciplinary irons. Neither label changed the substance of the interdisciplinary research it promoted. (Of course, if you can come up with still another name, you, too, can also come up with another “First Conference on....”)

The first sustained program of research were the studies of Russian investigators on the classical conditioning of immune responses. This research, derived from a Pavlovian perspective, began with Metal’nikoff and Chorine⁴ who were working at the Pasteur Institute in Paris. This research was reviewed in English in 1933 by no less than Clark Hull,⁵ a renowned learning theorist of that era. It was also reviewed in 1933 and, again, in 1941 by Kopeloff.^{6,7} The only other substantive review of this literature in English appeared in *Psychoneuroimmunology*.⁸ None of these early reviews attracted much attention or had any impact on research outside the then Soviet Union, including the studies of brain lesions on immune reactions and the physiologic studies of stress derived from the work of Hans Selye. Even the research implicating the nervous system in the modulation of immune responses initiated by Rasmussen and his colleagues and others in the 1950s and 60s failed to attract much sustained attention from any but a few behavioral scientists.

Aaron Frederick Rasmussen, Jr. was certainly one of the earliest pioneers of psychoneuroimmunology. His association with Norman Brill, then Chair of the Department of Psychiatry at the UCLA School of Medicine, was probably the first collaboration between a microbiologist/immunologist and a behavioral scientist. Rasmussen died in 1984, at the age of 68, after serving as Chair of the Department

of Medical Microbiology and Immunology (1962-1969) and thereafter as Associate Dean of the School of Medicine. He is remembered as a beloved and inspiring teacher and colleague and an outstanding virologist whose genetic studies laid the foundation for understanding the notorious worldwide variability in influenza viruses. Rasmussen was a meticulous experimental microbiologist, who, at the same time, never lost sight of host factors in disease. He was intrigued by the unproved conventional wisdom that emotional states influence the course of infectious illness, as depicted by such great novelists as Thomas Mann and as observed by such great pre-modern clinicians as Sir William Osler. An integrative thinker not bound by disciplinary lines, Rasmussen sought out Brill to discuss his “psychomicrobiological” ideas.

In 1957, Rasmussen, Marsh and Brill demonstrated that a stressful experience, avoidance conditioning, could increase the susceptibility of mice to herpes simplex virus. In a series of landmark papers, the pathogenic effect of emotional stress on animals exposed to herpes virus,⁹ Coxsackie B virus,¹⁰ and vesicular stomatitis virus¹¹ was explored. He and his coworkers also found decreased susceptibility to poliomyelitis virus in stressed monkeys, an early demonstration of the variability in stress effects on disease susceptibility.¹² Anticipating modern work in psycho-oncology as well as psychoneuroimmunology, Rasmussen and his colleagues also found that stress influenced the malignancy of polyoma virus in mice,¹³ and his later work on stress included measures of viral antibodies and interferon production.^{14,15} I regret very much that I never met Fred Rasmussen. His research set the stage for a variety of studies dealing with stress and infection, such as those initiated by Friedman, Glasgow and Ader,^{16,17} and Solomon’s studies on stress and antibody responses to a novel bacterial antigen.¹⁸ (It may not be scientifically noteworthy, but it is of personal interest that my colleague, Nicholas Cohen, was a postdoctoral student in Rasmussen’s department at UCLA

in the mid 1960s. Unfortunately, Rasmussen's involvement in this research was decreasing which may explain why it took Cohen so long to enter the field.)

George Solomon was another of the early investigators to show that psychological or environmental stressors could influence immunity. He and his colleague, Rudolf Moos, made painstaking observations of the life histories and personality characteristics of patients, seeking a clue to the frequently observed association between emotional states and the onset or exacerbation of arthritis. Solomon described the area as "psychoimmunology" and, despite the concerns of some of his colleagues, hung a sign to that effect on his laboratory door. In retrospect, Solomon's perspective on psychoneuroimmunology derived from curiosity, serendipity, psychodynamics, and the organization of disparate observations. Equally important, he claims, is the role of tenacity, frustration tolerance, and the ability to accept the encouragement of some and to reject the negativism of others in the development of new observations and theories.

Initially, Solomon was interested in psychological factors in the onset and course of autoimmune disease.¹⁹ This interest was instigated by his father, a psychiatrist, who was convinced that psychological factors played a role in the onset and course of rheumatoid arthritis. As a resident in psychiatry at the Langley Porter Institute, he and W. Jeffrey Fessel studied patients with systemic lupus erythematosus (SLE) who had severe psychiatric symptoms. The similarity of the symptoms in SLE to the symptoms seen in schizophrenia, prompted Solomon to ask whether schizophrenia could be an autoimmune disease of the brain with genetic and psychological predisposing factors that could be influenced by stressful life experiences. After a stint in the army, Solomon returned to the University of California in San Francisco and to research on immunoglobulins and schizophrenia.²⁰

He also joined forces and established a productive collaboration with Rudolf Moos, a psychologist, who was studying psychosocial factors in rheumatoid arthritis (RA). Solomon and Moos later joined the Department of Psychiatry at Stanford, but continued to do their research at UCSF; at Stanford, they encountered difficulties in obtaining access to arthritic patients for such “psychological nonsense.” The most unusual study in their series of papers on rheumatoid arthritis²¹ was the one comparing physically healthy relatives of RA patients (known to have a greater than average likelihood of developing autoimmune disease) with the RA patients themselves — with the additional consideration of whether or not their sera contained rheumatoid factor, an anti IgG antibody characteristic of rheumatoid arthritis. Neither subjects nor examiners knew the sera status of the study population. Those who were negative for the rheumatoid factor were like a general population: normally distributed from psychologically healthy to psychologically disturbed. However, rheumatoid factor positive relatives of RA patients were psychologically “healthy,” lacking anxiety, depression, or alienation and reporting good relationships with spouses, friends, and relatives. Psychological well-being seemed to exert a protective influence in the face of a probable genetic predisposition to autoimmune disease.

The future, Solomon thought, lay in mechanistic studies — and, what’s more, he saw an opening. In 1963, he read a paper by Robert Good²² who postulated a relationship between autoimmunity and relative *immunologic incompetence*. Frank Dixon²³ related such incompetence to the pathogenic formation of antigen-antibody complexes which occur when the amount of antibody is low in relation to antigen. Solomon immediately strung together: immunologic incompetence, adrenocorticosteroid hormones and immunosuppression with stress and corticosteroids. A naive and simplistic notion, he thought, but a heuristic one, nonetheless. These notions were presented in “Emotions, immunity, and disease:

A speculative theoretical integration” published in 1964.²⁴ Solomon attempted to conscript Moos into developing a laboratory in which they could stress rodents. “After all, no one,” he thought, “was going to believe clinical data, but they will be convinced by animal experiments.” Moos, however, was not an experimentalist and chose to pursue other interests, so Solomon was on his own. He was provided with a laboratory, but he recognized that he knew virtually no immunology. Practically all the immunologists with whom he spoke told him that the immune system was autonomous, totally self-regulatory, and, thus, not subject to neuroendocrine influences. Nevertheless, Solomon established his “psychoimmunology laboratory.” Although he had the support and tutelage of good people, he was unable to develop the necessary assay procedures for this work and considered giving up this line of research. Instead, he contacted one of the most noted immunologists in the world, Sir MacFarlane Burnet, who had revolutionized immunology with his clonal-selection theory of antibody formation. In response to Solomon’s letter, Sir MacFarlane Burnet replied: “I am most skeptical, but your ideas are interesting. Why don’t you come to Melbourne? We’ll talk, and my successor, Gus (now Sir Gustav) Nossal will teach you simple techniques for stress studies.” Solomon did go to Melbourne where he claims he learned something about immunology and a great deal about immunologists.

In the ensuing years, Solomon was able to enlist the collaboration of gifted colleagues with whom he conducted some of the first studies that now fall under the rubric of “psychoneuroimmunology.” With Thomas Merigan, who ran the tedious bioassay, he studied the effects of stress and steroids on interferon production.²⁵ Using flagellin, a bacterial antigen, it was shown that handling during early life could influence subsequent primary and secondary antibody responses in rats,²⁶ and that different stressors have different affects on antibody production.¹⁸ He also developed a collaboration with an immunologist, Alfred

Amkraut, whom Solomon describes as “brave, most competent, obsessively meticulous, and cautious.” Solomon and Amkraut studied the effects of stress on virus-induced tumors,²⁷ graft-vs-host reactions,²⁸ adjuvant-induced arthritis,²⁹ and other immunologic reactions. “Nobody, however, was listening.” Among other things, “Alfred was not given tenure (‘What does the CNS have to do with immunology?’).” Thus, in the early 1970’s, Solomon closed the door on this line of research. Ten years later, however, he was to return.

Solomon kept close watch on the developments in psychoneuroimmunology, “...especially after the publication of Ader and Cohen’s conditioning work.” Having been asked to contribute to the first edition of *Psychoneuroimmunology*, he concluded that “PNI was on the map at last,” and returned to the field. AIDS was suspected of being infectious, it involved immune abnormality, and it could also affect the CNS. AIDS, then, seemed the ideal condition to study within a psychoneuroimmunologic frame of reference. In 1983, Solomon moved from Fresno to the home campus of the University of California in San Francisco to join the incipient biopsychosocial AIDS project designed to seek psychologic-immunologic (AIDS progression) correlations. There he pursued his long-standing interest in “exceptions to the rule,” namely long-term survivors with AIDS from whom he felt one might learn what psychological factors and mediating mechanisms contributed to health and longevity. Their informally studied group of long-term survivors were remarkable people.³⁰ One of these was singer Michael Callen who wrote about the study in his book, *Surviving AIDS*. Callen, who died in 1994 after 12 years of symptomatic AIDS, personified what Solomon was attempting to explain. Another personal encounter that colored Solomon’s perspective on psychoneuroimmunology was his association with Norman Cousins. It was Cousins’ interest in understanding the role of attitude in healing that led L.J. (“Jolly”) West, then Chair of the Department of Psychiatry

and Biobehavioral Sciences, to invite Solomon to join the faculty at the University of California in Los Angeles. Cousins founded a UCLA Task Force on Psychoneuroimmunology of which Solomon is still a member. In addition to continuing work on AIDS, Solomon is currently engaged in some psychologically “upper” research: research on “very healthy old people instead of sick young people.”

One of the channels of communication between the neuroendocrine and immune systems is achieved through the receptors that exist on immune cells. John Hadden was prompted to ask if lymphocytes had adrenergic receptors by the emergence of adenylate cyclase as the beta receptor transduction unit in many tissues and, most specifically, by “The beta adrenergic theory of the atopic abnormality in bronchial asthma” proposed by Ando Szentivanyi.³¹ Based on studies in guinea pigs of the effects of hypothalamic lesions and stimulation on anaphylactic responses,^{32,33} the first of such studies on brain lesions and immune reaction, Szentivanyi suggested that the CNS had an impact on the immune system, at least in terms of allergic mechanisms. He further postulated a blockade of beta adrenergic receptors, with a resulting exaggeration of immune responses, as a cause of asthma. That is, it was hypothesized that beta adrenergic receptors acting via the adenylate cyclase/cyclic AMP system would down regulate allergic immune phenomena.

It was during his first year of a medical fellowship with Elliot Middleton, Jr. that Hadden learned of Szentivanyi’s formulation and set out to determine if lymphocytes had adrenergic receptors that could regulate immune function in a meaningful way. Hadden and his associates showed that, in the presence of hydrocortisone, alpha-adrenergic stimulation augmented and beta adrenergic stimulation inhibited the lymphoproliferative response to the mitogen, PHA.³⁴

This was the first observation linking lymphocytes to the sympathetic nervous system, opening a wide door to the study of neural influences on immunity.

These findings led Hadden in several directions. The notion that beta antagonists and cyclic AMP down-regulated lymphocyte proliferation was pursued by several investigators and confirmed for a variety of lymphocyte functions.³⁵ Hadden and his associates elaborated on the newly detected alpha adrenergic effects as these related to glucose metabolism and transmembrane K⁺ transport, finally linking them to direct effects on membrane ATPases of lymphocytes.³⁶⁻³⁸ While working in Minneapolis on transmembrane signaling, Hadden was introduced to cyclic GMP by Nelson Goldberg. Together, they found that cyclic GMP was involved in the signal induced in lymphocytes by PHA.³⁹ They also found that cyclic GMP was involved in lymphocyte cholinergic responses. While in the process of developing these observations, Terry Strom presented the first paper to show that T lymphocyte cytotoxicity was augmented by muscarinic cholinergic stimulation.⁴⁰ Hadden and his associates extended these results, demonstrating stimulation of RNA and DNA synthesis of lymphocytes and implicating cyclic GMP in the process.^{41,42} These observations were the first to link lymphocytes to the parasympathetic nervous system, opening a door to immune regulation by the entire autonomic nervous system.

Hadden initiated some additional *in vivo* studies, but became allergic to the animals and had to abandon this line of research. Besides, he was then preoccupied with questions about signal transduction mechanisms. He was not unmindful and, indeed, was fascinated by Robert Good's stories about his personal involvement in successful demonstrations of hypnotically-induced alterations of immunity,⁴³ but it appeared to him that the study of the neural modulation of immunity was not yet ready to surface as a bona fide area of research. Yet, it was in 1980 that Hadden, instrumental in the organization of the new International

Conferences on Immunopharmacology and starting a new journal, the *International Journal of Immunopharmacology*, invited me to present at this immunology meeting. It was important, he thought, that the immunopharmacologist be made aware of the research and the implications of the work on conditioning and immunity. “Now, 25 years later,” Hadden writes, “I recognize that it has emerged and I am happy to have contributed some impetus.” As evidenced by recent work on the endocrinology of the thymus,^{44,45} Hadden remains committed to an understanding of neuroendocrine-immune communication.

When asked how I became involved in psychoneuroimmunology, I can not refer to a logical starting point. I say it was an accident; I was “forced” into it by my data. I was studying taste aversion learning in rats. When a novel, distinctively-flavored conditioned stimulus (CS), saccharin, is paired with the unconditioned effects of a drug, cyclophosphamide (CY), which induces a transient stomach upset, the animal learns in one such conditioning trial to avoid saccharin-favored drinking solutions. We were conducting an experiment on the acquisition and extinction of the conditioned aversive response as a function of the strength of the CS, i.e., the volume of saccharin consumed before the animal was injected with CY. As expected, the magnitude of the conditioned response was directly related to the volume of saccharin consumed on the single conditioning trial. Also, repeated presentations of the CS in the absence of the drug resulted in extinction of the aversive response, and the rate of extinction was inversely related to the magnitude of the CS. However, in the course of these extinction trials, animals began to die. A troublesome but uninteresting observation. As more animals died, it became evident that mortality, like the magnitude of the conditioned response, varied directly with the volume of saccharin consumed on the one drug trial; a troublesome but interesting effect.

As a psychologist, I was unaware that there were no connections between the brain and the immune system. Therefore, I was free to make up any story I wanted in an attempt to explain this orderly relationship. The hypothesis was that, in the course of conditioning the avoidance behavior, we were also conditioning the immunosuppressive effects of cyclophosphamide. If, every time the conditioned animals were reexposed to the CS previously paired with the drug, the CS induced a conditioned immunosuppressive response, these animals might be more susceptible to low levels of pathogenic stimulation that may have existed in the laboratory environment. Moreover, if the strength of the conditioned response was a function of the magnitude of the CS, the greater the immunosuppressive response, the greater the likelihood of an increased susceptibility to environmental pathogens. Thus, it was the serendipitous observation of mortality in a simple conditioning study and the need to explain an orderly relationship between mortality and a conditioned aversive response that gave rise to the hypothesis that immune responses could be modified by conditioning operations.

A Letter to the Editor describing these observations and the speculation that immune responses were subject to conditioning was published in *Psychosomatic Medicine* in 1974.⁴⁶ It was a draft of this letter that elicited the first of many unexpected and sometimes frightening responses to this work. George Engel who, having criticized me for being too conservative in the past, said that, based on my conservative reputation, people were going to believe this, just because I said it. Although meant as a compliment, I found the prospect somewhat frightening; I had not given up my right to be wrong. I was to learn, however, that if you say something unimportant, it doesn't matter whether you're right or wrong; if, however, you say something that could be important, you had better be right!

People listened politely, but I did not have much luck in generating any interest in this hypothesis — let alone the help I would need to examine it — until I met

Nicholas Cohen. Cohen was the first person with sophistication in immunology who didn't think these notions were too "far out." Thus began a collaboration that is as active today as it was in 1974. Still oblivious of the Russian studies of the 1920s, Cohen and I designed a study to directly examine the hypothesis that immune responses could be modified by classical conditioning. For better or worse (sometimes, we're not sure), the first experimental paradigm we adopted was successful and, with some evident trepidation on the part of the reviewers and editor, "Behaviorally conditioned immunosuppression" was published in 1975.⁴⁷ This study demonstrated that, like other physiological processes, the immune system was subject to classical (Pavlovian) conditioning, providing dramatic evidence of an inextricable relationship between the brain and the immune system. Essentially, we were forced to the conclusion that there was a relationship between the brain and the immune system. The biomedical community, however, was, to be generous, guarded — and, to be precise, quite negative. Such a phenomenon simply could not occur because, as everybody knew, there were no connections between the brain and the immune system. Seminar groups were assigned the (unsuccessful) task of finding out what we had done wrong. The first replication of our findings⁴⁸ came from a study originally intended to show that, taking appropriate care and using more accurate assay procedures, the effect would not occur. The National Institutes of Health and National Institute of Mental Health, however, were not "forced" to the conclusion that one could condition alterations in immunologic reactivity, and, notwithstanding George Engel's predictions, Study Sections were loathe to use my conservative reputation as collateral. However, reading between the lines of "pink sheets" (and as confirmed by Study Section members much later), we might be right — and could they take that chance for so little money — and for only two years at a time? Our initial study was supported by a one-year grant from the Grant Foundation (where my

reputation was collateral) and then, reluctantly, it seems, we were funded by the NIH. At that time, ours was the only NIH grant in this area which, on renewal, was thereafter supported by the NIMH. Today, a computer search of “psychoneuroimmunology” and “neuroimmunomodulation” lists more than 200 active research grants being supported by the U.S. Public Health Service.*

Over the next several years, there were replications and major extensions of conditioned alterations of humoral and cell-mediated immune responses.⁴⁹⁻⁵¹ Recent work has successfully used antigen, itself, as the unconditioned stimulus. A classically conditioned enhancement of antibody production occurred when conditioned mice were reexposed to the conditioned stimulus in the context of reexposure to a minimally immunogenic dose of that same antigen.⁵² These and earlier experiments⁵³ documented the conditioning of immune responses, per se, in contrast to the conditioning of immunopharmacologic responses. Studies in New Zealand mice genetically susceptible to a systemic lupus erythematosus-like disease were used to demonstrate the biologic impact of conditioned alterations in immune responses. Substituting CSs for active drug on some scheduled treatment days delayed the onset of autoimmune disease using a cumulative amount of immunosuppressive drug that was ineffective by itself in altering the progression of disease.⁵⁴ Similarly, reexposure to a CS previously paired with immunosuppressive drug treatment prolonged the survival of foreign tissue grafted onto mice.^{55,56} Such results have yet to be verified in human patients. However, there has been one clinical case study describing the successful use of conditioning in reducing by one half the amount of cytoxan therapy received by a child with lupus.⁵⁷

To date, the neural, endocrine, or neuroendocrine mechanisms underlying conditioned alterations in immune function are unknown — reason enough, apparently, for some biomedical scientists to reject the phenomenon, itself, or, in

the case of *Nature*, to reject for publication a paper demonstrating conditioned *enhancement* of antibody production without even providing a review. One can only wonder about the implications of applying uniformly the criterion of having to identify “...the precise mechanisms involved in the phenomenon you observe...” in order to publish experimental results. Besides the fact that the precise mechanisms underlying behaviorally-induced changes in immune function are not known, it is also true that in only a few instances has the functional significance of the bidirectional communication pathways that have been identified among the nervous, endocrine and immune systems been determined.

To be sure, our studies were not always maligned. I recall, for example, the evening I met Lewis Thomas whom I have always thought of as the Montaigne of the biological sciences. After a brief exchange of pleasantries, Thomas said, “You sure are making life difficult for some people.”

“Well,” I answered, slowly — trying to think of an appropriate response, “as I read Lewis Thomas, that shouldn’t bother you.”

“It doesn’t,” he replied, “I love it!”

During these same years, Hugo Besedovsky was beginning his studies on endocrine-immune system interactions. Besedovsky was led into psychoneuroimmunology through a clinical route. Trained as a pediatrician at the Medical Faculty of Rosario in Argentina, he was confronted daily with patients with infectious and other diseases involving the immune system. Having been “hybridized” early in his training, Besedovsky naturally viewed the immune system as operating within the context of other physiological processes. Reflecting his pediatric training, his first studies in the early 1970s addressed endocrine influences on the immune and haematopoietic systems during ontogeny.⁵⁸ He focused on adrenocortical function which, at the time, was the only endocrine activity known to affect immunity. He discussed his interest in the

possibility that neuroendocrine mechanisms could contribute to immunoregulation with Professor Bernardo Houssay who encouraged him to work with Sir Peter Medawar in London. Medawar accepted but then could not accommodate Besedovsky in his laboratory because of illness, so he went to the Swiss Research Institute in Davos, Switzerland where he was fortunate to have Ernst Sorkin as a mentor and collaborator.

Besedovsky's research on the neuroendocrine regulation of immune responses was, and still is, based on the premise that immune responses are a part of integrated homeostatic mechanisms under the control of the nervous and endocrine systems. Thus, he reasoned, it should be possible to provide evidence that: (1) antigen exposure initiates a flow of information to neuroendocrine structures about changes in the activity of immune cells; (2) as a consequence of this information, an efferent neuroendocrine response should be elicited; and (3) this efferent response should have functional significance for immunoregulatory processes and host defenses.

Besedovsky and his colleagues proceeded to demonstrate in two animal species that, independent of any "stress-induced" responses related to the procedures, immunization with different antigens was capable of inducing endocrine changes (an increase in corticosterone and a decrease in thyroxin) that were under CNS control.⁵⁹ This was followed by a collaboration with Professor Dominik Felix from the Brain Research Institute in Zurich which established that there was, in parallel with the production of antibody, an increase in the firing rate of neurons within the ventromedial hypothalamus.^{60,61} This was a dramatic demonstration that the nervous system is capable of responding to signals emitted by an immune response. These results, Besedovsky recalls, were first submitted to *Nature* which rejected the paper "because it is self evident that the brain must receive information from the immune system."

Hugo Besedovsky's professional and personal relationship with Adriana del Rey, also from Argentina, began when she joined the Institute in Davos in 1977. Their first collaborative research concerned antigenic competition and the immunosuppressive role of elevations in adrenocortical steroids.⁶² These studies supported their hypothesis that glucocorticoid elevations associated with antigen exposure act to prevent an abnormal expansion of the immune response which might otherwise result in a cumulative, excessive immune cell proliferation favoring the expression of autoimmune and lymphoproliferative processes and the production of potentially harmful products of activated lymphocytes.

Analogous experiments on the involvement of the sympathetic nervous system in immunoregulation included the measurement of the content and the turnover rate of splenic noradrenaline during an immune response. In highly reactive animals, there is a decrease in noradrenaline content which occurs before the peak in antibody titers;^{63,64} animals that have a less active immune system show an increase in noradrenaline in lymphoid organs.⁶⁵ Also, corresponding to the increased activity of hypothalamic neurons during an immune response, Besedovsky and his associates⁶⁶ showed that there was a reduction in the noradrenaline turnover rate in the hypothalamus and brain stem. Clearly, there was a very dynamic interaction between the immune system and the sympathetic nervous system that influenced immunoregulatory processes.

The fact that there were endocrine, autonomic and neural activity changes during the course of immune responses indicated that the immune system could convey information to the CNS which led Besedovsky to suggest that the immune system acts as a "receptor sensorial organ."^{60,66} This implies that the CNS can sense the activity of the peripheral immune system involved in the recognition of non-self intruders and modified self-components, as well. If so, the products of immune cells should be able to affect neuroendocrine function. His approach

involved stimulating immune cells *in vitro* and transferring the supernatants obtained from such cultures into naive animals. The culture supernatants induced a pituitary-dependent increase in plasma corticosterone and a decrease in the content of noradrenaline in the brain of the rats.^{67,68} Thus, Besedovsky provided the first evidence that products of activated immune cells could affect endocrine responses that were under CNS control. When purified lymphokines and monokines became available in the 1980s, the laboratory began to study the capacity of these immune system mediators (e.g., interleukin-1) to influence neuroendocrine functions.^{69,70} Current research focuses on the effects of endogenously produced lymphokines and monokines.

Current research also includes a concern for the potential clinical relevance of neuroendocrine-immune system interactions. For example, some of the endocrine changes effected by the inoculation of tumor cells are mediated by cytokines rather than being a direct result of the tumor, itself, or the ensuing disease.⁷¹ Also, the pituitary-adrenal response to lipopolysaccharide is cytokine mediated⁷² and IL-1 is a main factor in activation of the pituitary-adrenal axis during viral infections.⁷³

The innovative research initiated by Hugo Besedovsky, Adriana del Rey and their colleagues has had a major impact on the acceptance of an integrated approach to research on homeostatic processes, in general, and on psychoneuroimmunology, in particular. It has also had a major impact on the conceptualizations and on the directions of research coming from several laboratories in the United States and in Europe. That, however, took time. Initially, the response to their work, like the response experienced by others in the field, was disheartening. On one of their several trips from Davos to Basel, Besedovsky and del Rey met with Niels Jerne, then Director of the Institute of Immunology, to discuss their ideas about the role of hormones and

neurotransmitters in immunoregulation with a world famous immunologist whom they admired greatly.

Jerne listened and said, “This is too complicated. We still do not know many things about the immune system, and I think we should know, for example, whether there is a T cell receptor. Maybe you should work *in vitro*...” Needless to say, this was an unexpected and upsetting response. About five years later, Besedovsky was giving a seminar at the Hoffman-LaRoche Laboratories where the first person to arrive was Neils Jerne. Following Besedovsky’s talk on the immunomodulating effects of glucocorticoids, Jerne stood up and said that “I have always believed that there is a communication between the immune and endocrine systems and ...”

Adriana del Rey, sitting near Jerne, interrupted him and shouted: “This is not true! Five years ago you told us...(and she repeated the story).”

Of course, Jerne laughed and said, “Well, what I meant to say was that I have always believed it but, after seeing these results, I think it may be true!” (Parenthetically, Nicholas Cohen, who had spent a sabbatical year at the Basel Institute in 1975, was invited to review our work on conditioning for a 1981 volume⁷⁴ honoring Neils Jerne.)

Besedovsky is now Professor of Physiology in the Medical Faculty of the University of Marburg in Germany where he has established a Department of Immunophysiology. The multidisciplinary expertise of his research group is still devoted to investigations of the complex immune-neuro-endocrine interactions that characterize the physiology of the immune system.

Similar thinking was directing the research of Edwin Blalock when, in 1979, lymphocytes were discovered to be a source of brain peptide neurotransmitters and pituitary hormones.⁷⁵ These observations were the unexpected culmination of three years of research when, as an Assistant Professor of Microbiology at the

University of Texas Medical Branch in Galveston, Blalock started out to determine if the cytokine, interferon (IFN), could function as a hormone. Indeed, it appeared that, among its other endocrine activities, interferon preparations could stimulate the adrenal to synthesize glucocorticoids.⁷⁶ Since the sequences of IFN were not known at the time and IFN was functioning like ACTH, the primary regulator of the adrenal gland, Blalock and his first postdoctoral fellow, Eric Smith, wondered whether the steroidogenic activity of the cytokine might be due to the presence of a residue ACTH-like sequence within the IFN molecule. Although this appeared to be so,⁷⁵ further studies, including the cloning of IFN, showed that this was not the case.⁷⁷ But, this research led to an even more remarkable finding: supernatant fluids from human lymphocytes cultured with IFN contained ACTH and the endogenous opioid peptides, endorphins.⁷⁷ —Blalock remembers quite vividly the exhilaration they felt on the day they first observed immunofluorescent pictures of lymphocytes staining positively for the production of these substances. Such observations were indeed surprising since, at the time, these peptides were thought to be the exclusive property of the brain and pituitary gland. For Blalock — and for many others in the developing field of psychoneuroimmunology — this discovery suggested a molecular approach for solving the mystery of how the mind could control the immune system, e.g., how classical conditioning might modify immunity. Such a relationship could exist because the body's two principle recognition organs, the brain and the immune system, speak the same chemical language. If true, this meant that the immune system could, indeed, talk back to the brain and, perhaps, alter physiology and behavior. Research accomplished in the last several years confirms the fact that such relationships do, in fact, exist^{78,79} and, because of the molecular and biochemical nature of these studies a large measure of respectability was given to psychoneuroimmunology — but, not immediately.

As with most, if not all discoveries that challenge current dogma, Blalock's work was met with healthy as well as unhealthy skepticism and, like many pioneers in the field of psychoneuroimmunology, the messengers suffered personal and professional indignities. The NIH site visitors reviewing their first research grant proposal in this area concluded that Blalock and his colleagues were actually sane and that the work had merit, but the project was funded for only two years. According to Blalock, the study section's message was clear: you must sequence the lymphocyte's ACTH to make your point unequivocally. In retrospect, this was considered an impossible request made by Study Section members who, according to Blalock, had never, themselves, sequenced anything. However, as "green" investigators, who were also referred to as "biochemical yahoos," Blalock and his associates did not know enough to be daunted. After a year of research and encouraging results, the Study Section members were still unimpressed and Blalock's application for renewal of this research was disapproved. When later reviewed by scientists knowledgeable in the area, this very same proposal was judged to be in the top 5% of all the grants reviewed at that time. Given the time and resources, Blalock and his colleagues were able to sequence the peptides which were found to be authentic.⁸⁰ Other investigators began to pay attention and the study of neuroendocrine-immune system communication took another giant step. Today, it is accepted that brain peptides and their receptors exist within the immune system and that the products of an activated immune system function as neurotransmitters. Thus, the scientific pariahs became heroes (apparently, they have not yet experienced unreferenced descriptions of these phenomena prefaced by the phrase, "As we have long expected..."). The process, agonizing at times, was rewarding and intellectually stimulating, but, as Blalock puts it: the scientific enterprise would be more

enjoyable if the scientific community recognized that “science is about unexpected discovery, not expected results.”

Another critical link between the brain and the immune system was forged by David Felten. He and his colleagues brought anatomical, neurochemical, receptor-binding, and *in vitro* and *in vivo* immunological techniques to bear on this relationship and provided unequivocal evidence that sympathetic noradrenergic nerve fibers signal cells of the immune system and are capable of evoking major changes in their responsiveness. Again, it was a serendipitous observation that altered the direction of Felten’s research.

In 1980, Felten was examining a section of rodent spleen with fluorescence histochemistry for catecholamines to distinguish arterial and venous patterns of smooth muscle innervation. He saw and reported extensive networks of noradrenergic sympathetic nerve fibers among T cells in the white pulp, and was confused about why this had not been described in the past.⁸¹ Felten had always looked at interactions among neuronal systems in a non-traditional fashion. From his early work at MIT as an undergraduate in Walle J.H. Nauta’s laboratory, he was fascinated with integrative regulatory neuronal systems. His unexpected observation of sympathetic noradrenergic nerve fibers in apparent direct contact with lymphocytes and macrophages thus fell on fertile ground. He and his colleagues proceeded to show that these nerve fibers were localized in precise compartments of both primary (thymus, bone marrow) and secondary (spleen, lymph nodes) lymphoid organs,⁸¹⁻⁸⁴ and formed close, synaptic-like neuro-effector junctions with T lymphocytes and macrophages.⁸⁵

Felten recalls that his early findings were ridiculed by many immunologists and viewed with disbelief as “minor aberrations,” at best. However, with characteristic energy and persistence, he and his collaborators spent several years investigating and demonstrating that these noradrenergic nerve fibers fulfilled the

criteria for neurotransmission with cells of the immune system with thymus, spleen, and lymph nodes as targets. In a detailed developmental study, it was shown that these nerve fibers formed these close contacts with lymphocytes early in ontogeny, and appeared to influence early immunological development and compartmentation.⁸⁶ At the other end of the lifespan, sympathetic nerve fibers in secondary lymphoid organs were found to diminish markedly with age.⁸⁷ Felten has proposed that this loss contributes to immunosenescence, particularly to diminished T cell functions, especially TH1 (cell-mediated) responses. In other recent work, Felten's laboratory demonstrated that local denervation of adrenergic sympathetic nerves from draining lymph nodes in autoimmune disease-susceptible rats enhanced joint inflammation and bone erosion in adjuvant-induced arthritis, while selective denervation of substance P nerve fibers from such draining lymph nodes protected the rats from joint pathology.⁸⁸ Such findings substantiate the functional importance of nerves supplying lymphoid organs.

In 1983, Felten was awarded a prestigious John D. and Catherine T. MacArthur Foundation Prize Fellowship at the early stage of his work in neural-immune interactions. Parenthetically, this was one of the Foundation's few ventures into psychoneuroimmunology. Several discussions and conferences in the early days held out the prospect that such new, interdisciplinary research would meet the original criteria for MacArthur Foundation support: innovative research that would face difficulties in finding support from within traditional federal funding agencies. Perhaps, however, it was too soon; purportedly, the advice received by the Foundation at that time was that psychoneuroimmunology wasn't going anywhere. David and Suzanne Felten, however, were going to the Department of Neurobiology and Anatomy at the University of Rochester School of Medicine and Dentistry to team up with Bob Ader, Nick Cohen and Sandy Livnat to develop interdisciplinary programs of research and research training.

In demonstrating a major role for sympathetic noradrenergic nerve fibers in regulating immune functions, Felten and his colleagues provided evidence for a direct, “hard-wired” connection between the CNS and the immune system. This connection has since been shown to be a major route for behavioral influences and for central cytokine influences on immune function. For Felten, the demonstration of direct neural signaling of cells of the immune system opens up several completely new directions for research. It is now possible to seek the chemical and receptor-mediated mechanisms by which behavioral and other CNS influences on immune responses are achieved. He and his colleagues are pursuing the use of neurotransmitter agonists and antagonists to specifically manipulate sites of initiation of immune responses, development and regulation of effector cell functions, and modulation of effector cell functions at diverse sites. Felten’s work is a cornerstone of a mechanistic understanding of the signaling between the nervous and immune systems and provides a basis for understanding the complex systemic integration among behavioral processes, the brain, and immunophysiology.

Thus, it was during the 1970s and early 80s that independent lines of research, derived as much from the personal experiences and imagination of the investigators as from a logic dictated by different disciplinary perspectives, began converging on the theme that the immune system was part of a larger, integrated mechanism of homeostatic processes serving the survival interests of the individual. For whatever reasons — and despite overt and covert resistance — this was evidently the right stuff at the right time! A new picture of immunoregulatory processes was emerging that promised a new understanding of the functions of other narrowly conceptualized systems and a new appreciation of the multi-determined etiology of pathophysiological states. A paradigm shift was occurring and, as a result of the nearly twenty years of research precipitated by the

above findings, it is no longer possible to study immunoregulatory processes as an independent function of the immune system. The research initiated by these investigators were giant steps and, despite the fact that they originated from different perspectives, they had a common effect. There were earlier, isolated studies, but most of the current research in the field derives directly or indirectly from these seminal studies. These were enabling studies in the sense that they raised questions and, further, legitimized questions that had not been asked before. And if these questions — and, sometimes, the questioners — were ridiculed, another almost universal experience, the evidence was, first, compelling, and then overwhelming. Thus, as Schopenhauer observed, “All truth passes through three stages. First it is ridiculed. Second it is violently opposed. Third it is accepted as being self evident.” This has almost become a cliché, yet a recent textbook in immunology⁸⁹ devotes a section to neuroendocrine-immune system relationships and concludes that, “Clinical and experimental psychoneuroimmunology studies to date confirm the *long-standing belief* that the immune system does not function completely autonomously.” (Italics added).

It is the research conducted during the past 20 years that probably accounts for 95 per cent or more of what is now known about the relationships among behavioral, neural and endocrine, and immune processes of adaptation³ and led to the general (and sometimes still begrudging) acknowledgment that, like other physiological processes operating to protect the organism, the immune system is part of an integrated system of adaptive processes and is thus subject to some regulation by the brain. Two pathways link the brain with the immune system: autonomic nervous system activity and neuroendocrine outflow via the pituitary. Both routes provide biologically active molecules which are perceived by the immune system via cell surface or internal receptors on the surface of lymphocytes, monocytes/macrophages and granulocytes. Thus, all

immunoregulatory processes take place within a neuroendocrine milieu that is demonstrably sensitive to the influence of the individual's perception of and response to events occurring in the external world.

Conversely, we have learned that activation of the immune system is accompanied by changes in hypothalamic, autonomic, and endocrine processes, and by changes in behavior. For example, cytokines influence activation of the hypothalamic-pituitary-adrenal (HPA) axis — and, in turn, are influenced by glucocorticoid secretion.⁷⁰ The potential interaction of neuroendocrine and immune processes is further magnified by the fact that cells of the immune system activated by immunogenic stimuli are capable of producing a variety of neuropeptides.⁹⁰ Thus, the exchange of information between the brain and the immune system is bidirectional.

Based on the above, it is hardly surprising that behavioral factors are capable of modifying immune function or that activation of the immune system would have consequences for behavior. The Pavlovian conditioning of the suppression or enhancement of immune responses⁵¹ and, conversely, the conditioning of the physiological effects of cytokines⁹¹ both reflect adaptive immunoregulatory processes. The majority of the behavioral research, derived in large measure from the work of Hans Selye, has addressed the immunologic effects of stressful experiences. Early studies concentrated on the immunosuppressive effects of adrenal gland activation. These pharmacologic and physiologic studies were complemented by the behavioral studies of Rasmussen's group in the 1950s, by Friedman and Ader and by Solomon in the 1960s and by a host of others, primarily physiologists, during this same time period.^{92,93} There was not a lot of research of this kind from the late '60s until the publication of *Psychoneuroimmunology*.² In the 1980s, however, "stress and immune function"

was revived and, armed with a modern technology, became the dominant theme of the behavioral component of psychoneuroimmunology.

Human studies of the immunologic changes associated with emotional states and stressful life experiences also took shape in the 1980s. Stimulated by a description of some of the immunologic effects of sudden bereavement,⁹⁴ researchers began to address the effects of losses (e.g., the death of a spouse) and of affective states, particularly, depression, on immunity. For example, Marvin Stein, then Chair of the Department of Psychiatry at the Mt. Sinai Hospital and Medical Center in New York, had, during the 1960s, been actively involved in studies of the effects of hypothalamic lesions and stimulation on anaphylactic reactions in guinea pigs.⁹⁵ Like Solomon, Stein returned to psychoneuroimmunology in the 1980s with a program of animal research on the immunologic effects of stressful experiences and a program of human studies of the immunologic changes associated with loss and with depression. In this, Stein was able to engage an interdisciplinary team of young investigators (and to stimulate the interest of several others) who now have psychoneuroimmunology laboratories of their own.

Similarly, the unique team of Janice Kiecolt-Glaser, a psychologist, and Ronald Glaser who, as Chair of a Department of Medical Microbiology and Immunology, entered the field with considerable apprehension, initiated an extensive series of studies that began with the effects of examinations in medical students on changes in immunity.⁹⁶ Glaser, like many others, became convinced of the role of behavioral factors in the modulation of immunity only when he found such relationships in his own data. Although a common event in the life of students, examination periods were found to be reliably associated with a general depression of immune function including, as a consequence, an elevation in antibodies to Epstein-Barr virus. These studies were directly and indirectly

responsible for a reemergence of animal and human studies by behavioral scientists and by immunologists on the effects of stressful life experiences on immune function and susceptibility to infectious diseases.

In animals and in humans, a variety of psychosocial events interpreted as being stressful to the organism are capable of influencing a variety of immune responses. It is now clear, however, that different “stressors” have different effects on some constant outcome measure and that the same “stressor” can have different effects on different outcome measures. The direction, magnitude and duration of stress-induced alterations of immunity are influenced by: (a) the quality and quantity of stressful stimulation; (b) the capacity of the individual to cope effectively with stressful events; (c) the quality and quantity of immunogenic stimulation; (d) the temporal relationship between stressful stimulation and immunogenic stimulation; (e) sampling times and the particular aspect of immune function (or compartment) chosen for measurement; (f) the experiential history of the individual and the existing social and environmental conditions upon which stressful and immunogenic stimulation are superimposed; (g) a variety of host factors such as species, strain, age, sex, and nutritional state; and (h) interactions among these several variables. This listing of relevant variables identified in recent research paraphrases the variables identified from a much earlier analysis of the effects of stressful life experiences on behavioral and physiological responses and on susceptibility to disease.^{17,97} Indeed, prospective as well as retrospective studies in animals and humans have also shown that, depending on interactions among the qualitative and quantitative nature of the environmental demands and the pathophysiologic process, the experimental procedures, and a variety of host factors, stressful experiences can alter the host’s defense mechanisms thereby altering susceptibility to bacterial and viral infections, modifying the neuroinvasiveness of normally non-neurovirulent strains of virus, or allowing an

otherwise inconsequential exposure to a pathogen to develop into clinical disease.^{1,98,99}

The behavioral and emotional states that attend the perception of and the effort to adapt to environmental circumstances are accompanied by complex patterns of neuroendocrine changes. That the neural and endocrine patterns associated with behavioral and emotional states are capable of modulating immune functions lends credence to the hypothesis that changes in immune function constitute an important mediator of the pathophysiological effects of stressful life experiences. This chain of psychophysiological events may not yet have been firmly established, but, as this volume attests, the possibility is attracting renewed attention and the data are providing evidence of the relevance of psychosocially-induced alterations in immune function for differences in the susceptibility to and progression of infectious diseases.

Where is psychoneuroimmunology today? It's still working out some adolescent problems and on its way to young adulthood. It has not yet achieved the maturity of neuroendocrinology or the more recent psychoneuroendocrinology — and it has not been granted the scientific respectability it has earned and to which it is entitled. Still, psychoneuroimmunology continues to grow. *Brain, Behavior and Immunity* began publishing in 1987 and there are now two other journals devoted to the area. Research reports are now considered (and solicited) for publication in a variety of peer reviewed journals in immunology, psychology and in the neurosciences, including endocrinology. There are now two international societies and papers in the field occupy increasing blocks of time at the meetings of other scientific societies. There has been an increase in the number of students (including M.D./Ph.D. candidates) from psychology, immunology and the neurosciences interested in working in the area, and there has been an increase in the number of funded research and research training grants.

There has also been a proliferation of edited volumes that address various aspects of the field (e.g., *Psychoneuroimmunology*, *Stress and Infection*).

Psychoneuroimmunology is, perhaps, the most recent example of an interdisciplinary field that has developed and now prospers by exploring and tilling fertile territories secreted by the arbitrary and illusory boundaries of the biomedical sciences. Disciplinary boundaries and the bureaucracies they spawned are biological fictions that can restrict imagination and the transfer and application of technologies. They lend credence to Werner Heisenberg's assertion that "What we observe is not nature itself, but nature exposed to our method of questioning." (p. 81).¹⁰⁰ Our own language, too, must change. The signal molecules of the nervous and immune systems are expressed and perceived by both systems. Therefore, it may no longer be appropriate to speak of "neurotransmitters" and "immunotransmitters." Also, to speak of links or channels of communication between the nervous and immune systems perpetuates the myth that these are discrete systems (or disciplines). On the contrary, the evidence indicates that relationships between so-called "systems" are as important and, perhaps, more important than relationships within "systems;" that so-called "systems" are critical components of a single, integrated network of homeostatic mechanisms. To the extent that the problems chosen for study and innovative research strategies to address these problems derive from conceptual and theoretical positions, these are important issues.

More substantively, research conducted over the past several years has resulted in a recognition and appreciation of the interactions among behavioral, neural, endocrine, and immune processes. Indeed, there has been a paradigm shift in the attempt to understand immunoregulatory function. The innervation of lymphoid organs and the availability of neurotransmitters for interactions with cells of the immune system add a new dimension to our understanding of the

microenvironment in which immune responses take place. Similarly, the interaction between pituitary-, endocrine organ-, and lymphocyte-derived hormones that define the neuroendocrine milieu in which immune responses occur adds another level of complexity to the analysis of the cellular interactions that drive immune responses. Collectively, these relationships provide the foundation for previously observed behaviorally-induced alterations in immune function and for immunologically based changes in behavior. They may also provide the means by which psychosocial factors and the emotional states that accompany the perception and response to stressful life experiences influence the development and progression of infectious, autoimmune and neoplastic disease.

ACKNOWLEDGMENTS

I am grateful to Drs. Hugo Besedovsky, J. Edwin Blalock, John Hadden, and George Solomon for providing for me a brief written description of their perspectives on psychoneuroimmunology and for their comments and corrections of an earlier draft of this paper. I am also indebted to Dr. Sherman M. Melinkoff, Professor Emeritus of Medicine and former Dean of the UCLA School of Medicine for his personal reflections of A. Fred Rasmussen. Thanks are also due to my colleagues, Drs. David Felten and Nicholas Cohen who contributed material for this essay. The responsibility for the selection of these particular perspectives, the editorializing, and any remaining errors are my own.

Preparation of this paper was supported by a Research Scientist Award (K05 MH06318) from the National Institute of Mental Health.

FOOTNOTES

*As I write this chapter, it seems evident that the financial support for research in psychoneuroimmunology, despite its successes, will face serious difficulties over the next several years (but that's a different chapter).

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