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On the development of psychoneuroimmunology

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Abstract

Psychoneuroimmunology, the study of interactions among behavioral, neural and endocrine, and immune processes, coalesced as an interdisciplinary field of study in the late 1970s. Some of the early research that was critical in establishing neuroanatomical, neurochemical and neuroendocrine pathways and functional relationships between the brain and the immune system is outlined here. These and subsequent studies have led to the general acknowledgment that the nervous and immune systems are components of an integrated system of adaptive processes, and that immunoregulatory processes can no longer be studied as the independent activity of an autonomous immune system. This paradigm shift in the study of immunoregulatory processes and the elaboration of the mechanisms underlying behaviorally induced alterations of immune function promise a better understanding and a new appreciation of the multi-determined etiology of pathophysiological states.

Keywords: Conditioned response; Immunity; Stress; Psychoneuroimmunology

The immune system was once considered a self-regulating, autonomous agency of defense, critical in defending the organism against the invasion of foreign material. Indeed, at one time, the immune system was defined as that agency of defense that was independent of the nervous system. Research, most of which has been conducted over the past 25 years, however, has revealed that immunoregulatory processes are in reality influenced by the brain and, conversely, that neural and endocrine functions and behavior are influenced by the immune system. Psychoneuroimmunology is the study of the interactions among behavior, neural and endocrine function, and immune system processes. The neologism was first used in 1980, in my presidential address to the American Psychosomatic Society (Ader, 1980). Its most conspicuous use was as the title of an edited volume (Ader, 1981a), prophetically described as "the signature volume of a new field of research." The central premise of this interdisciplinary field is that adaptation is the product of a single, integrated network of defenses. Each component of this network evolved to serve specialized functions. These are the parochial interests of the "disciplines" into which we have divided the biological sciences. At the same time, though, each component of this defensive network monitors and responds to information derived from the others. Thus, we cannot fully understand immunoregulatory processes without considering the organism and the internal and external milieu in which immune responses take place.

The notion of integration is neither new nor controversial. Psychopharmacology acknowledges that drug effects depend on the state of the organism into which they are introduced. Neuroendocrinology accepts that endocrine function can only be understood in the context of its interactions with the nervous system. Psychoneuroendocrinology acknowledges that the feedback and feedforward pathways between these "systems" influence and are influenced by behavior. Psychoneuroimmunology, then, is merely one of the newest of the hybrid disciplines necessitated, in this instance, by the need to more fully understand immunoregulatory processes. How this complementary strategy surfaced is the subject of this paper. Because I am a behavioral scientist, you should recognize that this account of the development of psychoneuroimmunology

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places some emphasis on behavior, and that while the key discoveries would remain the same, the relative amount of attention given to one or another area of research would undoubtedly vary with the storyteller.

Psychoneuroimmunology is usually dated by the publication of the first edition of Psychoneuroimmunology in 1981. Thereafter, volumes with more or less specific foci (mostly based on conference proceedings) have been published at a rapid rate (Guillemin et al., 1985; Berczi, 1986; Plotnikoff et al., 1986, 1991; Berczi and Kovacs, 1987; Cotman et al., 1987; Perez-Polo et al., 1987; Goetzl and Spector, 1989; Freier, 1990; Husband, 1991, 1993; Blalock, 1992; Schmoll et al., 1992; Glaser and Kiecolt-Glaser, 1994; Scharrer et al., 1994; Lewis et al., 1994; Leonard and Miller, 1995; Friedman et al., 1995; Marsh and Kendall, 1996; Rabin, 1999). As one might expect, though, the study of brain-immune interactions began before then — well before then. But, I'm already getting ahead of myself — not in terms of the chronology of events — but in the way the field developed, which are not the same thing.

For my part, I was, in the early 1970s, studying taste aversion conditioning in rats. Taste aversion learning is a variant of classical Pavlovian conditioning. It is an extremely robust one-trial, passive avoidance learning situation in which a novel, distinctively flavored drinking solution, the conditioned stimulus (CS), is paired with the unconditioned effects of a drug that has noxious (e.g., gastrointestinal) consequences, the unconditioned stimulus (UCS). Under these circumstances, the animal will learn, after a single CS–UCS pairing, to avoid consumption of the CS solution. In our study, rats drank different volumes of a saccharin solution and were then injected with a constant dose of cyclophosphamide, an immunosuppressive drug that had been used in studies of taste aversion learning because it induces the desired gastrointestinal upset. As expected, the magnitude of the conditioned aversive response was directly related to the volume of saccharin consumed on the single conditioning trial. Also, repeated CS presentations without the drug extinguished the avoidance behavior, and the rate of extinction was inversely related to the magnitude of the CS. Unexpectedly, animals began to die in the course of these extinction trials — a troublesome but not a particularly interesting observation. It soon became evident, however, that like the magnitude of the conditioned response, mortality rate varied directly with the amount of saccharin the rats consumed on the one conditioning trial — a troublesome but interesting observation.

As a psychologist, I did not know there were no connections between the brain and the immune system. I was therefore free to consider any possibility that might explain this orderly relationship between the magnitude of the conditioned response and the rate of mortality. The hypothesis that seemed reasonable from a behavioral perspective was that, in addition to conditioning the avoidance response, we were conditioning the immunosuppressive effects of cyclophosphamide. If reexposure to a CS previously paired with an immunosuppressive drug evoked a conditioned immunosuppressive response, and if the strength of the conditioned response was a function of the magnitude of the CS, these animals might have been more susceptible to otherwise subthreshold levels of pathogenic stimulation existing in the laboratory environment. Thus, the serendipitous observation of mortality in a simple conditioning study and the need to explain an orderly relationship between mortality and the conditioned avoidance behavior prompted the hypothesis that immune responses could be modified by classical conditioning.

Colleagues persuaded me to write a letter to Psychosomatic Medicine describing these observations and the hypothesis that immune responses were subject to conditioning. I asked Dr. George Engel to read a draft of the letter (from which I had deleted the title in order not to create any expectation about its contents). Engel, who had previously criticized the Discussion sections in my research papers for being overly cautious, predicted that my conservative reputation was now going to pay off: people were going to believe this just because I was the one who said it. Although it was meant as a compliment, I found the prospect somewhat unnerving. I wanted my ideas to be considered, of course, but, in my own defense, I also wanted to retain my right to be wrong. This was but the first of many unexpected and sometimes frightening responses to this work. I was to learn, however, that if you say something that is not especially important, it does not matter whether you are right or wrong; but, if you say something that could be important, you had better be right!

The Letter to the Editor in Psychosomatic Medicine (Ader, 1974) did not, as far as I know, attract any attention or generate any interest in testing the hypothesis. The exception was Nicholas Cohen, an immunologist, who thought the preliminary observations should be pursued. Using the taste aversion conditioning model, he and I designed a study to determine if immune responses could be modified by classical Pavlovian conditioning. The results: conditioned animals that were reexposed to a CS, saccharin, previously paired with the immunosuppressive effects of cyclophosphamide (the UCS) showed an attenuated antibody response to sheep red blood cells compared with conditioned animals that were not reexposed to the CS, nonconditioned animals that were exposed to saccharin and a placebo-treated control group. With some evident apprehension on the part of the Program Committee and the Editor of the journal, the manuscript, "Behaviorally conditioned immunosuppression" was presented at the meetings of the American Psychosomatic Society and published in Psychosomatic Medicine that year (Ader and Cohen, 1975).

The results of this initial experiment demonstrated that, like other physiological processes, the immune system was subject to classical conditioning, thereby documenting a

functional relationship between the brain and the immune system. In that paper, we wrote that:

> ...there may be an intimate and virtually unexplored relationship between the CNS and immunologic processes and that the application of behavioral conditioning techniques provides a means for studying this relationship in the intact animals. Confirmation of the capacity of behavioral conditioning procedures to suppress (or elicit) immune responses would raise innumerable issues regarding the normal operation of and modifiability of the immune system in particular and the mediation of individual differences in the body's natural armamentarium for adaptation and survival in general. Such data also suggest a mechanism that may be involved in the complex pathogenesis of disease and bear eloquent witness to the principle of a very basic integration of biologic and psychologic function. (Ader and Cohen, 1975, pp. 338–339).

The publication of these data did attract attention and generate interest in some quarters. For the most part, though, the biomedical community was less than enthusiastic. Such a phenomenon was not possible because the immune system is an autonomous agency of defense; there are no connections between the brain and the immune system. Seminars were frustrated in their attempts to identify flaws in the study, and some critics found solace using the rationalization that so many control groups were required and that statistics were needed to document the effects. Of course, such remarks came to us by word of mouth; none of these "arguments" were ever put into print.

Over the next several years, there were replications and major extensions of the work on conditioned alterations of immune function (Ader and Cohen, 1993). The first replication of our results (Rogers et al., 1976) was a study originally intended to show that, with appropriate care and more accurate assay procedures, the effect would not occur. There is now an extensive literature documenting the acquisition and/or extinction of conditioned nonspecific host defense responses (e.g., natural killer (NK) cell activity) and different antibody- and cell-mediated responses using different unconditioned and conditioned stimuli. Conditioning is not confined to changes associated with taste aversion learning; several studies have described the acquisition and extinction of conditioned "stress" effects. Also, conditioned immunosuppressive responses cannot be attributed to stress-induced or conditioned elevations of adrenocortical steroids.

More recently, we have used antigens, the most salient stimuli for activating the immune system, as UCs. A classically conditioned enhancement of antibody production was observed when conditioned mice were reexposed to the CS in the context of reexposure to a minimally immunogenic dose of that same antigen (Ader et al., 1993). Others (Alvarez-Borda et al., 1995) have observed a one-trial conditioned enhancement of antibody responses without further exposure to antigen and we (unpublished data) have since confirmed these findings. These and earlier studies (Gorczynski et al., 1982), are demonstrations of conditioned immune responses as opposed to conditioned immunopharmacologic responses.

The biologic significance of conditioned alterations of immune function has been addressed in studies of lupus-prone mice. A suppression of immune function is in the biological interests of these animals. The substitution of CS for active immunosuppressive drug on half the weekly treatment days delayed the onset of autoimmune disease using a cumulative amount of drug that was not sufficient, by itself, to influence progression of the autoimmune disease (Ader and Cohen, 1982). Similarly, re-exposure to a CS previously paired with immunosuppressive drug treatment protected animals against the development of adjuvant-induced arthritis (Klosterhalfen and Klosterhalfen, 1983; Lysle et al., 1992) and prolonged the survival of foreign tissue grafted onto mice (Gorczynski, 1990; Grochowicz et al., 1991). Such results have not been experimentally verified in human patients, but there is one clinical case study of conditioning in the treatment of a child with systemic lupus erythematosus (Olness and Ader, 1992).

The neural, endocrine, or neuroendocrine mechanisms subserving conditioned alterations of immunity are unknown. For some biomedical scientists, that is sufficient grounds for rejecting the data on conditioning or, more broadly, the reality of behaviorally induced alterations of immune function. An editorial in Nature (Maddox, 1984) entitled, "Psychoimmunology before its time," being a case in point. A rejoinder, originally entitled, "Psychoneuroimmunology — it's about time," (Ader and Cohen, 1985) was eventually published after a compromise was reached on the title. Nonetheless, a study on conditioned immunoenhancement was subsequently rejected by Nature. Like many submissions, it was not judged to be of sufficient general interest in existing categories to justify review. Also (incidentally), our (nonreviewed) paper failed to identify "...the precise mechanisms involved in the phenomenon you observe..." The uniform application of this criterion would most certainly solve what many people believe is the problem of too many scientific journals.

For the sake of balance, I hasten to add that our studies were not always maligned. Indeed, they were enthusiastically received by many individuals. I enjoy describing one example: the evening I met Lewis Thomas whom I consider 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!"

Although we were not aware of it at the time, Russian investigators had initiated studies on the classical con-

ditioning of immune responses in the 1920s (e.g., Metal'nikoff and Chorine, 1926). Indeed, this was the first sustained program of research on brain–immune system interactions. Derived directly from a Pavlovian perspective on the conditioning of behavioral and physiological responses (Pavlov, 1928), a CS (e.g., heat, tactile stimulation) was repeatedly paired with injections of foreign proteins. Subsequent exposure to the CS, alone, was purported to induce antibody production in addition to a conditioned increase in a variety of nonspecific defense responses.

Most of this research was published in Russian. It was reviewed in English language journals (Hull, 1934; Kopeloff, 1941), but attracted little attention outside the Soviet Union. Within the Soviet Union, it provoked heated arguments. Many early investigators believed that an antibody response was the direct result of neural activity, i.e., that the nervous system, by itself, could stimulate antibody production. The majority of the scientific community rejected that proposition (and, thus, the possibility of conditioning immune responses). By today's standards, most of these early experiments on conditioning were inadequately described and poorly designed, but they did yield interesting preliminary data. The studies on nonspecific immunologic reactions, for example, yielded reasonably consistent evidence of conditioning. The evidence for the conditioned production of antibody, however, was less convincing. A detailed review, including statistical reanalyses of some of the data, was furnished by Ader (1981b).

Other early indications of central nervous system (CNS) influences on immunity came from studies of hypothalamic lesions or stimulation and anaphylactic responses. Szentivanyi and Filipp (1958) and Szentivanyi and Szekely (1958) were among the first to show that hypothalamic lesions could prevent anaphylactic shock in animals. Studies conducted during the 1960s and 1970s yielded a sometimes inconsistent pattern of results. In the early 1980s, this avenue of research was revisited by several investigators, particularly Tom Roszman and his associates who described changes in several parameters of immunity as a result of anterior hypothalamic interventions (e.g., Roszman and Carlson, 1991). Studies on posterior interventions were less consistent. The evident need for and the increasing availability of techniques with more specificity undoubtedly contributed to the apparent demise of this research strategy.

Stimulated by Szentivanyi's early lesion work and the possible involvement of beta adrenergic activity in bronchial asthma, John Hadden set out to determine if lymphocytes had adrenergic receptors that could regulate immune function. Hadden et al. (1970) showed that alpha adrenergic stimulation potentiated, and beta adrenergic stimulation inhibited the lymphoproliferative response to the mitogen, phytohemagglutinin (PHA). This link between lymphocytes and the sympathetic nervous system and the idea that beta antagonists and cyclic AMP downregulated lymphoproliferative responses was thereafter pursued by several investigators. Hadden also found that cyclic GMP was involved in the signal induced in lymphocytes by PHA and in lymphocyte cholinergic responses (Hadden et al., 1972). At the same time, Strom and his colleagues showed that T lymphocyte cytotoxicity was augmented by muscarinic cholinergic stimulation (Strom et al., 1972). These were some of the earliest observations linking lymphocytes to the parasympathetic nervous system and, thus, immunoregulatory processes to the autonomic nervous system.

One of the earliest pioneers in the study of behavioral influences on immunity was Fred Rasmussen, a microbiologist. Intrigued by the suspicion that emotional states could influence the development or course of infectious illness, Rasmussen enlisted the behavioral expertise of Norman Brill, a psychiatrist — probably the first such collaborative team — to initiate a program of research on stress and infectious disease. During the 1950s and 1960s, Rasmussen and his colleagues examined the effects of avoidance conditioning, physical restraint, electric shock, and social "crowding" on mice inoculated with herpes virus (Rasmussen et al., 1957), vesicular stomatitis virus (Jensen and Rasmussen, 1963), and Coxsackie B virus (Johnson, et al., 1965) and on poliomyelitis virus in monkeys (Marsh, et al., 1963). Some of this work also included measures of viral antibodies and interferon (INF) production (Chang and Rasmussen, 1965; Yamada et al., 1964). Susceptibility to viral infections was increased or decreased, depending on the nature of the stressor. These studies, with implications for nervous system modulation of immunity, also failed to attract much general attention, although they were forerunners of some of the research initiated by a few persistent investigators (e.g., Amkraut et al, 1971; Friedman et al., 1965, 1969; Solomon, 1969; Solomon et al., 1968).

Another pioneer in the development of psychoneuroimmunology was George Solomon. Solomon's initial clinical research examined the life histories and personality characteristics of patients with autoimmune disease. In what is probably the best known of their studies, Solomon and Moos (1965) compared rheumatoid arthritis patients with their "at risk," but healthy, relatives. An additional dimension of their analysis was the presence or absence of rheumatoid factor, an anti IgG antibody characteristic of rheumatoid arthritis. For those who were negative for the rheumatoid factor, psychological "health" was normally distributed. Compared to the patients, however, relatives who were rheumatoid factor positive were psychologically "healthy," lacked anxiety, depression, or alienation and reported good relationships with spouses, relatives and friends. Psychological well being seemed to have had a salutary effect in the face of the probable genetic predisposition to autoimmune disease.

Convinced that experimental research would be more persuasive, Solomon established a "psychoimmunology"

laboratory and studied the effects of behavioral, social and endocrine manipulations in animals on immune function and responses to a bacterial antigen, virus-induced tumors, and adjuvant-induced arthritis (reviewed in Solomon and Amkraut, 1981). As in other such studies, the effects varied as a function of the stressor and the outcome measure chosen for study. "Nobody, however, was listening," Solomon believed, and, in the early 1970s, he discontinued this line of research — temporarily. Ten years later, he returned to the field and adopted a psychoneuroimmunologic perspective in a program of clinical research on AIDS.

During the 1970s, Hugo Besedovsky was beginning to piece together a neuroendocrine–immune system network with his studies of the effects of immune responses on neural and endocrine function. If, as he viewed it, immune function was integrated with other physiological processes, exposure to an antigen should be evidenced by changes in neuroendocrine activity that, in turn, should have feedback effects on immunoregulatory processes and host defenses. Besedovsky et al. (1975) demonstrated that immunization with different antigens was capable of inducing CNS-derived endocrine changes. They also found that, following immunization, there was an increase in the firing rate of neurons within the ventromedial hypothalamus at a time corresponding to the time of peak production of antibody (Besedovsky et al., 1977). This dramatic demonstration that the nervous system could perceive and respond to signals emitted by an activated immune system was first submitted to Nature, which rejected the paper because "it is self evident that the brain must receive information from the immune system."

There followed a series of studies on the immunosuppressive effects of corticosteroids, providing evidence that glucocorticoid elevations in response to antigenic stimuli might act to prevent an excessive expansion of immune responses that might promote the expression of autoimmune dysregulations. Analogous experiments on sympathetic nervous system involvement in immunoregulation revealed a decrease in splenic noradrenaline content in highly reactive animals, whereas animals with a less active immune system showed an increase in splenic noradrenaline (Besedovsky et al., 1979; del Rey et al., 1982). Also, there was a reduction of noradrenaline turnover rate in the hypothalamus and brain stem that corresponded with the increased activity of hypothalamic neurons in response to antigenic stimulation (Besedovsky et al., l983).

The evidence that changes in endocrine, autonomic and neural activity accompany immune responses supported the suggestion that the immune system acts as a "receptor sensorial organ." (Besedovsky and Sorkin, 1977). That is, the CNS can sense the behavior of the peripheral immune system in its recognition and response to immunogenic stimuli. It should be possible, then, for products of activated immune cells to influence neuroendocrine function. The transfer of supernatants obtained from cultures of in vitro stimulated immune cells induced a pituitary-dependent increase in plasma corticosterone and a decrease of noradrenaline in the brain of naive rats (Besedovsky et al., 1981, 1985). Thus, Besedovsky and his colleagues provided the first evidence that products of activated immune could influence endocrine responses that were under CNS control.

The innovative research initiated by Hugo Besedovsky and his 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. Initially, however, the reactions to their work (e.g., "...it's too complicated.") was disheartening. Niels Jerne, who first considered their efforts to be misdirected, later qualified his remarks about the relationship between the immune and endocrine systems by saying that "...I have always believed it, but, after seeing these results, I think it may be true!"

Similar thinking guided the research of Edwin Blalock when, in 1979, lymphocytes were found to be a source of brain peptides and pituitary hormones (Blalock and Smith, 1980). Originally, Blalock asked if the cytokine, IFN, could function as a hormone. In the course of these studies, it was found that supernatant fluids from human lymphocytes cultured with IFN contained adrenocorticotropic hormone (ACTH) and endogenous opioid peptides, endorphins (Smith and Blalock, 1981). These observations were quite remarkable, since at the time, these peptides were thought to reside exclusively in the brain and pituitary. This discovery suggested that there might be a molecular approach to understanding how behavior could influence the immune system, e.g., how classical conditioning might modify immunity. This relationship could exist if the brain and immune system spoke the same chemical language and thereby communicated with each other (Blalock, 1984).

Again, the work of Blalock and Smith, like most innovations that challenge current dogma, was met with some appropriate and some inappropriate skepticism, the latter being coupled with perceived personal and professional indignities. Eventually, however, the sequencing of lymphocyte-derived peptides (Smith et al., 1990) and other, more recent studies (Blalock, 1994) indicated that such intimacies between the brain and the immune system do, in fact, exist. The molecular and biochemical nature of these studies afforded a large measure of respectability to psychoneuroimmunology. Investigators from other disciplines began to pay attention and the study of neuroendocrine–immune system interactions 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.

Another critical link between the brain and the immune system was forged by investigators documenting and tracing the source of "hard-wired" connections from the nervous system to the immune system. Bulloch and Moore

(1981), for example, described brain stem and spinal cord innervation of a primary lymphoid organ, the thymus. David Felten unexpectedly observed and described extensive networks of noradrenergic sympathetic nerve fibers lying in direct contact with lymphocytes and macrophages (Williams et al., 1981). He and his collaborators in Rochester showed that these nerve fibers were localized in specific compartments of primary (thymus, bone marrow) and secondary (spleen, lymph nodes) lymphoid organs (Felten et al., 1987), and formed close, synaptic-like neuroeffector junctions with T lymphocytes and macrophages (Felten and Olschowka, 1987). It was also shown that these innervation patterns were formed early in the course of development and appeared to influence the ontogeny of immune function (Ackerman et al., 1991). At the other end of the lifespan, there was a marked diminution of the sympathetic innervation of secondary lymphoid organs (Bellinger et al., 1992), hypothesized to contribute to immunosenescence.

Using anatomical, neurochemical, receptor-binding, and in vitro and in vivo immunological techniques, neurobiologists have generated unequivocal evidence that sympathetic noradrenergic nerve fibers signal cells of the immune system and are capable of evoking major changes in their responsiveness. These "hard-wired" connections between the brain and the immune system have since been shown to be a major route for behavioral and for central cytokine influences on immune function. They are, thus, a cornerstone for a mechanistic understanding of the signaling between the nervous and immune systems.

It was these independent lines of research, derived from empirical observations rather than a logic dictated by current theory, that began to converge on the theme that the immune system was but one component of a larger, integrated system of defenses serving the adaptive interests of the individual. There were earlier, isolated studies to be sure. Following from the work of Selye (1950), for example, it was known that hormones, principally adrenocortical steroids, could influence immunity and "stress" (glucocorticoid) effects occupied the attention of a few physiologists. Some investigators were aware that brain lesions could influence immune responses. It was known, or at least suspected, that emotional states were associated with the development or progression of disease, including those involving the immune system. Few scientists took such observations too seriously, however. With the exception of the immunosuppressive effects of corticosteroids, there were no "mechanistic" explanations for how such things could come about. For whatever reasons, these isolated efforts never coalesced into a scientific presence of any kind.

The research initiated in the 1970s and early 1980s, however, was apparently "the right stuff at the right time!" No one study was (or could have been) responsible for psychoneuroimmunology. In fact, it is likely that no one study would have had quite the same impact had it not been for the converging evidence of brain–immune system interactions that was appearing in the literature at about the same time. These initial studies were enabling in the sense that they legitimized questions that had not been asked before. And if the questions — and, sometimes, the questioners — were disparaged, a common experience, the data were, at first, compelling, and soon thereafter, undeniable. Thus, the coalescence of research initiated during the 1970s — and the identity provided by the label, psychoneuroimmunology — reactivated latent interests and attracted new investigators to this nascent field.

Stimulated in large part by the report of Roger Bartrop and his colleagues describing immunologic changes associated with the bereavement that followed the sudden death of a spouse (Bartrop et al., 1977), several laboratories launched studies of the immune changes that were associated with emotional states and stressful life experiences. In particular, researchers addressed the effects of losses (e.g., the death of a spouse) and of affective states, particularly, depression, on immune function. For example, Marvin Stein, who had studied the effects of hypothalamic lesions and stimulation on anaphylactic reactions in guinea pigs during the 1960s (Stein et al., 1981), 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.

Like Vernon Riley, a microbiologist, working in the area in the 1970s (Riley et al., 1981), Ronald Glaser, a virologist, became convinced of the role of behavioral factors in modulating immune responses in human subjects only when he and Janice Kiecolt-Glaser, a psychologist, found such relationships in their own data (Kiecolt-Glaser and Glaser, 1991). Concentrating, initially, on a common stressful event in the life of medical students, they found that examination periods were associated with a general depression of immune function. In particular, there was an elevation in antibodies to the ubiquitous Epstein Barr virus, indicative of poorer cell-mediated control of the latent virus. They also described the pattern of changes in neuroendocrine and immune responses that occurred among caregivers for Alzheimer patients and among men and women who responded negatively to marital conflict. These are populations in which they also observed elevations in antibody titers to the latent Epstein Barr and herpes type 1 viruses, poorer responses to vaccinations, and a delay in the healing of experimentally induced wounds (Glaser and Kiecolt-Glaser, 1997; Glaser et al., 1998). It was in the 1980s, then, that studies of stress and immune function were revived and, armed with a modern technology, became the dominant focus of the behavioral component of psychoneuroimmunology.

There is now a voluminous literature on the immunologic effects of stressful life experiences (see Rabin, 1999; Ader and Cohen, 2000, for recent reviews). Only some

broad conclusions are possible here. In animals and humans, a variety of psychosocial events that are perceived to be stressful to the organism are capable of influencing cell-mediated and humoral immune responses as well as nonspecific host defense reactions. However, the concept of "stress" permits few generalizations. The direction, magnitude and duration of the effects of "stress" depend on the qualitative and quantitative nature of and the temporal relationship between the immunogenic and stressful stimulation, the primary or secondary responses being measured and a variety of host factors. Therefore, we are not always able to predict the immunologic effects of stressful life experiences. Nonetheless, the available data demonstrate that stressful life experiences can influence immune function, increase or decrease susceptibility to immunologically mediated diseases, permit an otherwise inconsequential exposure to some viruses to progress into manifest disease, or contribute to the reactivation of latent viral infection. Most of these data come from animal studies (e.g., Moynihan and Ader, 1996; Sheridan et al., 1994). Only a minority of studies in humans contains measures of both immune function and disease susceptibility. It remains to be definitively established, then, that an altered susceptibility to disease is the direct result of biologically relevant changes in immunocompetence induced by stressful life experiences.

> Psychoneuroimmunology is an interdisciplinary field of study that has developed and now prospers by exploring and tilling fertile territories secreted by the arbitrary if not illusory boundaries between the biomedical sciences. Disciplinary boundaries and the bureaucracies they created are biological fictions that can restrict imaginative research and the transfer and application of technologies. They lend credence to Heisenberg (1958) assertion that 'What we observe is not nature itself, but nature exposed to our method of questioning. (p. 81) (Ader, 1995, p. 17).

Research conducted over the past 25 years successfully challenged the commonly held assumption of and, thus, research strategies predicated on an autonomous immune system. In its place, a new picture of immunoregulatory processes has emerged that adds dimensions to the functions of other narrowly conceived systems and offers a new appreciation of the multi-determined etiology of pathophysiological states.

We are now aware that there are at least two pathways through which the brain and the immune system communicate: autonomic nervous system and pituitary-derived neuroendocrine activity. Both pathways generate chemical signals that are recognized by receptors on the surface of lymphocytes and other immune cells, and the activation or interruption of these signals influence immunologic reactivity. It is within this internal milieu — a neuroendocrine environment demonstrably sensitive to the individual's perception of and adaptive responses to events occurring in the external world — that immune processes, like other physiological processes, take place. Conversely, we have learned that activated lymphocytes produce neuropeptides and hormones that are perceived by the nervous system as reflected in further changes in hypothalamic, autonomic, and endocrine responses — and by changes in behavior. Cytokines, messenger molecules released by activated immune cells, regulate cellular interactions within the immune system but also influence and are influenced by the hypothalamic–pituitary–adrenal axis (Berkenbosch et al., 1987). Although the precise site(s) at which cytokines act within the brain remains to be identified, the behavioral effects of cytokines, particularly with respect to sickness behavior and cognitive functions has become a major focus of current research in psychoneuroimmunology (e.g., Dantzer et al., 1999).

In view of these findings of bidirectional communication between the brain and the immune system, it is hardly surprising that Pavlovian conditioning or stressful life experiences are capable of influencing immune function and the development and/or progression of immunologically mediated disease processes. The data with respect to conditioning are quite reliable, generalizable to both humoral and cell-mediated immune responses, and large enough or persistent enough to be clinically significant. But, the models in which conditioning effects have been studied have not yielded effects that are large enough to permit one to proceed easily to the next stage of questions that need to be addressed, primary among which would be the immunologic specificity of the conditioned responses. The data with respect to stressful life experiences are also quite reliable. As indicated, they are also quite complex and defy any simple characterization of their immunologic effects — or the clinical consequences of those immunologic effects.

The existence of these bidirectional pathways between the brain and the immune system reinforces the hypothesis that immune changes could constitute an important mechanism through which psychosocial factors influence health and disease. For the present, however, this remains a hypothesis. Depression, for example, is a risk factor for disease and depressed patients show a decline in both enumerative and functional measures of immunity (Herbert and Cohen, 1993). It has not been demonstrated, however, that the health effects of depression or other affective states are the direct result of biologically relevant changes in immune function. Similarly, the association between stressful life experiences and susceptibility to disease and the association between stressful life events and changes in immunocompetence do not establish a causal chain linking stress, immune function, and disease.

There are few studies in humans in which manifest disease has been shown to be a direct result of biologically relevant, behaviorally induced changes in immune function. There are, however, provocative animal models of experimentally induced or spontaneously occurring dis-

eases that address this issue. For example, stressful experiences delay virus-specific antibody production in mice infected with influenza and suppress NK cell activity and the development of cytotoxic T lymphocytes in animals inoculated with herpes simplex virus (HSV) (Sheridan et al., 1998). A disruption of the social hierarchy within a mouse colony increases agonistic behavior, activates the hypothalamic–pituitary–adrenal axis, and reactivates latent HSV in a significant proportion of latently infected animals (Padgett et al., 1998). In an NK-sensitive tumor model, several different stressors have been found to decrease NK cell activity and increase lung metastases (Ben Eliyahu et al., 1999).

The argument that the effects of behavioral factors on immune function are too "small" to be of clinical significance has been uncritically embraced. The idea that a CS or a stressful experience could, in the absence of other circumstances, perturb the immune system to an extent that exceeded homeostatic limits and lead to overt disease is a simplistic notion immunologically and behaviorally. On the contrary, the complexity of the cellular interactions involved and the feedback and feedforward pathways within and between the immune and nervous systems, the only behaviorally induced response that could reasonably be expected is one that would not exceed homeostatic limits. However, it is quite reasonable to suggest that behaviorally induced neuroendocrine changes capable of altering biologically relevant immune responses would have clinical consequences when interacting with environmental pathogens, when superimposed upon an existing pathology, or when immunocompetence is in some way compromised. Thus, appropriate research strategies for evaluating the potential importance of psychoneuroimmunologic interactions might take advantage of individual differences; high risk populations such as the aged, the immunocompromised, those with a genetic predisposition to a particular disease, or those with latent disease; the systematic variation of the magnitude of the immunogenic challenge to provide sufficient latitude for the observation of interaction effects; and the measurement of responses that are biologically relevant to particular disease processes.

The central premise underlying psychoneuroimmunology is that the nervous, endocrine, and immune system are components of an integrated system of defenses. Accepting this proposition could change the way we define and approach the study of certain diseases. It may not be too speculative to suggest that immunological strategies may offer keys to the understanding and treatment of behavioral, neural and endocrine disorders. Conversely, behavioral, neural and/or endocrine interventions could be relevant in the treatment of immune system-related diseases. Indeed, such strategies are already being suggested (Woody et al., 1999) or may be derived from existing data (Levine et al., 1984).

Despite the dramatic findings of functional relationships between the brain and the immune system gathered over the past 25 years, the neuroendocrine (let alone molecular) mechanisms underlying conditioned or stressor-induced changes in immune function have not been identified. The neural and endocrine changes that accompany changes in behavioral states and the network of brain–immune system connections that have already been elaborated provide numerous pathways through which behavioral processes could influence immune responses. And there is reason to believe that multiple pathways will be involved. These are likely to depend on the pattern of responses elicited by the unique nature of experiential factors as opposed to the common features of a nonspecific stress response (e.g., corticosteroid elevations) as well as the specific nature of the defensive responses elicited by the immunogenic challenge to which the individual is exposed. The clinical implications of psychoneuroimmunology will be better appreciated when we are able to identify and manipulate the interacting variables that govern immunoregulatory processes.

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