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Twenty years of psychoneuroimmunology and viral infections in *Brain, Behavior, and Immunity*

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Abstract

For 20 years, *Brain, Behavior, and Immunity* has provided an important venue for the publication of studies in psychoneuroimmunology. During this time period, psychoneuroimmunology has matured into an important multidisciplinary science that has contributed significantly to our knowledge of mind, brain, and body interactions. This review will not only focus on the primary research papers dealing with psychoneuroimmunology, viral infections, and anti-viral vaccine responses in humans and animal models that have appeared on the pages of *Brain, Behavior, and Immunity* during the past 20 years, but will also outline a variety of strategies that could be used for expanding our understanding of the neuroimmune–viral pathogen relationship.

1. Introduction

It is common in the course of a literature review to comment on the important and perhaps unique scientific contributions made by an individual researcher or groups of researchers with interests in the same or related disciplines. It is rare, however, to have the opportunity to review and comment on the impact that a journal has had on a field of scientific inquiry. The journal *Brain, Behavior, and Immunity* was created and has expanded and matured as the discipline of psychoneuroimmunology has become a truly multidisciplinary science. Found within the pages of *Brain, Behavior, and Immunity* over the past 20 years are studies describing the interactions among the nervous, endocrine, and immune systems in health and disease. From these studies, we have learned that behaviorally induced modulation of the immune response, through the activation of various neuroendocrine pathways, contributes to susceptibility to infection and disease pathogenesis. This review focuses on the studies of viral infections and anti-viral vaccines in humans and animal models that have appeared on the pages of *Brain, Behavior and Immunity* during the past 20 years.

In the early days of research into neuroendocrine–immune interactions and their role in viral-associated diseases, the significance of the studies demonstrating incremental changes in immunity was frequently questioned by editors and reviewers of mainstream journals representing disciplines such as immunology and virology. The field of psychoneuroimmunology has had to deal with questions such as, ''What does it matter that the natural killer cell response was reduced by 15 to 20 percent in the course of a stressful situation?'' and ''Is the response of peripheral blood mononuclear to concanavalin A stimulation really a good measure of the host's response to a behavioral challenge?''. Recognition that the immune system has built-in redundancies and that its efficacy can be ably expressed over a broad range of functions supported the validity of such questions. Over the years, as psychoneuroimmunology matured as a discipline and technological advances enhanced the ability to measure immune

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responses, *Brain, Behavior, and Immunity* provided a venue for studies that addressed these issues of validity.

To viral immunologists interested in regulation of the immune response by the products of the nervous and endocrine systems, it was clear that one of the best ways to address such questions about the relevance of incremental changes in immunity was to expose the host to an infectious pathogen and to determine if an experimental situation (stress, behavioral manipulation, hormonal treatment, pharmacologic blockade of neuroendocrine pathways, etc.) affected viral-induced pathophysiology or viral replication by modulating pathogen-specific immune function. Thus, such studies could determine if these interactions among the nervous, endocrine, and immune systems contributed to host resistance to viral infection. This *in vivo* approach was also accompanied by studies of immune cell phenotypes and functions *in vitro* that provided additional information on the state of the immune system.

The development of *Brain, Behavior, and Immunity* provided a venue for peer-reviewed articles and insightful critiques by a cohort of reviewers and editors working to establish the validity of psychoneuroimmunology-based research. While *Brain, Behavior, and Immunity* was not the only journal to publish psychoneuroimmunology-related papers, it was unique in that psychoneuroimmunology-based research was its primary focus. Investigators in psychoneuroimmunology came to understand the commitment that *Brain, Behavior, and Immunity* had to publishing high-quality papers that would support the continuous development of the field. Now in its 20th year, *Brain, Behavior and Immunity* publishes primary research papers, mini-reviews, named series, and special issues that are topically focused. This review will focus on primary research papers dealing with psychoneuroimmunology, viral infections, and anti-viral vaccine responses.

2. Decade 1—1987–1996

2.1. The viruses that were studied and why

Humans have long been afflicted with diseases caused by a variety of pathogenic microorganisms. Although the diseases caused by many of these pathogens are self-resolving as a result of a healthy immune system, some of these diseases (e.g., smallpox) may be deadly in the absence of any pre-existing immunity. Although the causative agents responsible for most infections were not identified until the mid-late 20th century, the roles of bacteria, fungi, viruses, and parasites in causing disease are now well defined. However, the mechanisms underlying a host's immune defenses against these pathogens, and the factors that control the magnitude of these responses, continue to be elucidated in laboratories across the world.

There are a number of microorganisms that are virulent and cause disease in humans resulting in significant morbidity and mortality. Thus, the impact of the neuroendocrine system on the immune response to any one of these pathogens is of interest to human health. The study of these pathogens could have provided the framework for the initial studies of neuroendocrine–immune interactions and the effect of these interactions on susceptibility to infectious disease. However, the pathogens that were examined in the early psychoneuroimmunology studies were primarily a function of the expertise and prior research endeavors of the investigators prior to their entry into this multidisciplinary field. For example, studies by a classical virologist, Ronald Glaser, whose initial research was with Epstein–Barr virus (EBV), a member of the herpesvirus family, was the first to determine the impact of psychological stress on the reactivation of EBV (Glaser et al., 1987, 1991). These virology-based studies were important in laying the foundation for additional studies pioneered by other scientists who received their initial training in the area of viral immunology. It was these latter studies that were among the first to determine the impact of stress on the immune response to, and pathogenesis of, herpes simplex virus type 1 (HSV-1) (Bonneau et al., 1991a,b; Bonneau, 1996), and influenza virus (Feng et al., 1991) infections in experimental rodent models.

EBV, HSV-1, and influenza virus were each known to have significant short- and long-term impact on human health and thus were important viruses to study in the context of psychoneuroimmunology. Furthermore, the prior development of versatile mouse models for studying HSV and influenza viral infections made the use of these viruses particularly attractive. Psychoneuroimmunology-related studies using these infection models facilitated the identification of immunological mechanisms that are modulated by activation of the neuroendocrine system. This work provided a foundation for more mechanistic studies of neuroendocrine–immune interactions.

The growing AIDS crisis and the identification of the human immunodeficiency virus (HIV) as the etiological agent of this disease during the initial decade of *Brain, Behavior, and Immunity* resulted in several key studies (Fisher et al., 1995; Nair and Schwartz, 1995; Pollack et al., 1996; Vitkovic et al., 1995). These studies examined the impact of psychosocial influences on HIV infection, immune function, and pathogenesis. Overall, one of the major strengths of these early virology-based studies in psychoneuroimmunology was the knowledge and expertise of the investigators in the area of viral immunology.

2.2. The immunological measures—the limitations, the variety, and those that were new

A number of human and animal studies that were published in this first decade of *Brain, Behavior, and Immunity* measured virus-specific immune function in terms of antibody titers (Glaser et al., 1987, 1991), primary and memory virus-specific cytotoxic T lymphocyte (CTL) responses (Bonneau et al., 1991a,b; Bonneau, 1996; Carpenter et al., 1994), natural killer (NK) cell activity (Nair and Sch-

wartz, 1995), and cytokine/chemokine production (Carpenter et al., 1994; Fisher et al., 1995; Vitkovic et al., 1995). A few of these studies (Bonneau et al., 1991a; Bonneau, 1996) made use of what was then the relatively new technology of fluorescent flow cytometry. These early studies were only able to utilize single-color analysis due to technological limitations at the time. However, the development of more sophisticated flow cytometers and powerful software for data acquisition and analysis, and the availability of an ever-increasing list of reagents, has allowed for the use of a variety of fluorescent markers for identifying, quantitating, and determining the functional activity of lymphocyte subsets. As noted below, the use of flow cytometry in the assessment of immune function significantly increased during the next decade and helped to better define the nature of neuroendocrine–immune interactions at the cellular level.

2.3. Modulators of anti-viral immunity—Models and mechanisms

While a wide variety of stress- and non-stress-associated neuroendocrine-derived peptides and hormones had been shown to modulate the immune response during viral infection, the data that linked psychological stress, immune modulation, and susceptibility to infectious microorganisms were weak. Consequently, many of the initial studies published in *Brain, Behavior, and Immunity* examined the impact of stress on viral infection (Bonneau et al., 1991a,b; Bonneau, 1996; Feng et al., 1991; Glaser et al., 1987, 1991). Early publications in this area also focused on the impact of academic stress on EBV reactivation in a population of medical students (Glaser et al., 1987, 1991). Although these and other human studies documented a link between stress and disease caused by infectious pathogens, it was the use of animal models of infection and immunity that enhanced our understanding of the neuroendocrine and immunological mechanisms underlying this link (Bonneau et al., 1991a,b; Bonneau, 1996; Feng et al., 1991).

The use of animal models in psychoneuroimmunology-related studies provided an opportunity to examine the effects of stress on the pathophysiology associated with each of these viral infections (Bonneau et al., 1991a; Feng et al., 1991). These early studies utilized a restraint model of psychological stress, thus leading to an interest in determining the role of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system as modulators of immune function. In addition, other studies (Carpenter et al., 1994) during this time period sought to identify neuroendocrine–immune interactions from the perspective of drug abuse by determining the impact of morphine/opioids on CTL function. Further uses of animal models included some of the first studies in which surgical manipulations, such as hypophysectomy (Dunn et al., 1987), were used to determine the specific components of the neuroendocrine system that were involved in the modulation of immune function. In a seminal study by Adrian Dunn and colleagues (Dunn et al., 1987) it was shown, through surgical manipulation, that a viral infection initiated neurochemical and endocrine responses that were observed during stress, and that such an infection alone could cause immunosuppression.

2.4. Brief summary of the decade 1987–1996

Of the 287 primary papers that were published in *Brain, Behavior, and Immunity* from 1987 to 1996, only 14 (5%) studied the impact of stress-induced activation of the HPA axis and neuroendocrine responses on the immune response during viral infections. However, these studies were critical in extending our understanding of neuroendocrine–immune communications and their impact on infection. Some of the mechanisms underlying the bi-directional communication between the neuroendocrine and immune systems were defined, and the contribution of bi-directional communication to defense during viral infection, began to be deciphered. Importantly, these studies established a foundation for studies that followed in the next decade (1997–2006).

3. Decade 2—1997–2006

3.1. "New" viruses and methods of "challenge"

The second decade of *Brain, Behavior, and Immunity* (1997–2006) saw a doubling in the number of papers that examined the relationship among the nervous, endocrine, and immune systems during infection and vaccination. While most psychoneuroimmunology-related studies using an experimental viral challenge were conducted in animals, one paper published in this decade described studies in which humans were deliberately infected with rhinovirus (Doyle et al., 2006). Other studies were conducted in which individuals were vaccinated with either the influenza virus (Edwards et al., 2006; Phillips et al., 2005, 2006) or hepatitis B virus (Marsland et al., 2006; Phillips et al., 2005) vaccine. Although these latter publications were not the first to identify a role for the neuroendocrine system in the immune response to vaccination in humans (Kiecolt-Glaser et al., 1996), they did provide further support that life events can indeed modulate the efficacy of vaccination.

While papers published in the first decade of *Brain, Behavior, and Immunity* described the impact of neuroendocrine responses on the control of acute, chronic, and latent viral infections, a number of papers in the second decade again employed many of these viruses including HSV-1 (Brenner and Moynihan, 1997; Glaser et al., 1999; Karp et al., 1997; Kohut et al., 2005; Lewandowski, 1997; Ortiz et al., 2003; Wonnacott and Bonneau, 2002; Yorty and Bonneau, 2004), EBV (Glaser et al., 2005; Pierson et al., 2005), influenza virus (Avitsur et al., 2006; Hunzeker et al., 2004; Swiergiel and Dunn, 1999; Toth and Hughes, 2004; Lowder et al., 2005; Tseng et al., 2005),

and HIV-related viruses (Capitanio et al., 1999; Kelley et al., 2002). Also studied for the first time were a couple of new viruses including a relatively new member of the *Herpesviridae* family of viruses, human herpesvirus 6 (HHV-6) (Glaser et al., 1999), and a hantavirus belonging to the *Bunyavirus* virus family, the Seoul virus (Hinson et al., 2006; Klein et al., 2002). Interestingly, there were also studies involving patients who were chronically infected with hepatitis C virus (HCV) (Raison et al., 2005). In addition, Theiler's virus, which produces symptomology in mice that is similar to multiple sclerosis, was first used as a model to examine the impact of stress on a disease with an autoimmune-based etiology (Campbell et al., 2001; Welsh et al., 2004).

3.2. The use of other neuroendocrine/stress models

Although a number of the animal model studies described in these publications continued to use restraint stress as a means to alter neuroendocrine profiles (Campbell et al., 2001; Hunzeker et al., 2004; Ortiz et al., 2003; Tseng et al., 2005; Welsh et al., 2004; Wonnacott and Bonneau, 2002; Yorty and Bonneau, 2004), other methods were also used including footshock (Brenner and Moynihan, 1997), social disruption, support and stability (Capitanio et al., 1999; Hinson et al., 2006; Phillips et al., 2005), and altered housing conditions (Karp et al., 1997). Human studies utilized novel models of stress such as spaceflight, (Pierson et al., 2005), cadet training (Glaser et al., 1999), and having subjects perform a series of mental tasks (Edwards et al., 2006)—all of which were potential stressors that could affect anti-viral immune function. Other possible modulators of anti-viral immune function that were studied included sleep (Toth and Hughes, 2004; Traynor et al., 2006), exercise (Edwards et al., 2006;Kohut et al., 2005; Lowder et al., 2005), sex hormones (Klein et al., 2002), depression (Raison et al., 2005), emotional style (Doyle et al., 2006), bereavement (Phillips et al., 2006), and positive affect (Marsland et al., 2006). Lastly, the impact of perinatal stressors on immune function was also investigated (Avitsur et al., 2006; Yorty and Bonneau, 2004). Overall, the findings in these studies served to underscore the importance of a variety of everyday life events in the modulation of anti-viral immunity.

3.3. Advances in immunology/virology and their application to psychoneuroimmunology-related studies

The field of immunology has steadily evolved with the advent of new and exciting methodologies for the detection and quantification of various aspects of immune function. As a result, our overall knowledge of the mechanisms underlying many facets of the immune response to viral infections has increased tremendously. Concomitantly, some of these methodologies and knowledge of immune function have been utilized in research efforts in the area of psychoneuroimmunology.

The previous decade has seen research in psychoneuroimmunology expand to include newly discovered cytokines such as IL-10 (Brenner and Moynihan, 1997; Kohut et al., 2005), the concept of Th1 and Th2 helper cell subsets and the associated cytokine balance (Karp et al., 1997; Marshall et al., 1998; Kelley et al., 2002), the use of RT-PCR for quantifying gene expression (Hunzeker et al., 2004; Raison et al., 2005), and the design of recombinant viruses for eliciting a single, protective component of an immune response against a specific pathogen (Wonnacott and Bonneau, 2002). The evaluation of immune responses in the draining lymphoid tissues, in the brain (Campbell et al., 2001; Lewandowski, 1997; Welsh et al., 2004), and at mucosal sites of viral infection (Wonnacott and Bonneau, 2002) represented new approaches to assess immune responses in psychoneuroimmunology-related research. Steady progress in defining the mechanisms underlying neuroendocrine-mediated immune modulation will require the application of these new technologies for studying immune function and our ever-growing base of knowledge of the many immunological processes that these technologies continue to reveal and that are seminal in eliciting a successful immune response.

3.4. The use of animal models—advantages in determining mechanisms

As indicated above, the use of animal models, particularly rodents, has well served the psychoneuroimmunology research community. The similarity of the murine immune system to that of humans, and the plethora of reagents that are readily available for detecting and quantifying various aspects of immune function, have made the use of these models ideal for determining the mechanisms underlying neuroendocrine–immune interactions. For example, a variety of studies have utilized chemical (e.g., sympathectomy) (Kelley et al., 2002), and pharmacological (RU486, nadolol, opioid receptor antagonists) (Kelley et al., 2002; Kohut et al., 2005; Ortiz et al., 2003; Tseng et al., 2005) approaches to determine these mechanisms in the context of anti-viral immunity. Thus, studies conducted in animal models in which specific components of the nervous, endocrine, and immune systems can be altered will continue to enhance our understanding of neuroendocrine–immune communications and their impact on resistance to infectious pathogens.

3.5. Brief summary of the decade 1997–2006

The studies described in the papers published during this epoch in *Brain, Behavior, and Immunity* established a strong foundation for the importance of neuroendocrine–immune interactions in anti-viral immunity and the response to vaccination. It should be emphasized that while *Brain, Behavior and Immunity* has disseminated timely and relevant information regarding neuroendocrine–immune interactions, there exists a number of other established

journals that also serve this highly interdisciplinary field of study. These other journals, with disciplines including one or more of those included in psychoneuroimmunology (e.g., immunology, neuroimmunology, neuroscience, physiology, psychology, psychiatry, microbiology, neurovirology), provide important information that aids in advancing knowledge of psychoneuroimmunology. Due to space limitations and the overall theme of this review, related papers published in these journals have not been included. The reader is directed to a number of reviews on this topic that have been published in the 178 chapters that have appeared in the four editions of the textbook, *Psychoneuroimmunology* (Ader, 1981, 2007; Ader et al., 1991, 2001).

4. 2007 and beyond

4.1. Achieving a better understanding of neuroendocrine immune modulation of viral pathogenesis

Our knowledge of neuroendocrine–immune interactions and their potential impact on viral pathophysiology has steadily grown over the past 20 years. This growth has continued to be fueled, in part, by research efforts that define the mechanisms underlying the bi-directional communications among the nervous, endocrine, and immune systems. Also contributing to this growth has been the intellectual and technological advances in each of the many individual disciplines that comprise the highly interdisciplinary field of psychoneuroimmunology. As illustrated in Fig. 1 and described below, these and other factors have, and will continue, to increase our understanding of the impact of the interactions among the nervous, endocrine, and immune systems and the ability of these interactions to modulate viral pathogenesis.

4.2. Pursuing the mechanisms

During the past 20 years, a modest number of papers published in *Brain, Behavior, and Immunity* have focused on the neuroendocrine-mediated modulation of anti-viral immunity. As outlined above, most of these papers examined the impact of various forms of psychological stress on anti-viral immunity and viral pathogenesis. An examination of these papers suggests that stress has a detrimental effect on the course and outcome of viral infections, and on the response to vaccination. To the readers of *Brain, Behavior, and Immunity*, this should come as no surprise. However, despite this progress, the cellular and molecular mechanisms underlying the relationship among stress, neuroendocrine activation, immune function, and viral pathogenesis have not yet been fully elucidated. Determining such mechanisms will be realized only as the experimental tools are developed to learn more about the basic immunological processes that are involved in resistance to viral pathogens. However, scientists in this domain of psychoneuroimmunology must be willing to embrace the use of these tools in their own research programs and do so in a timely fashion. Indeed, this willingness may be challenging given the already wide breadth and depth of each of the various disciplines that comprise the field of psychoneuroimmunology. However, it is expected that some

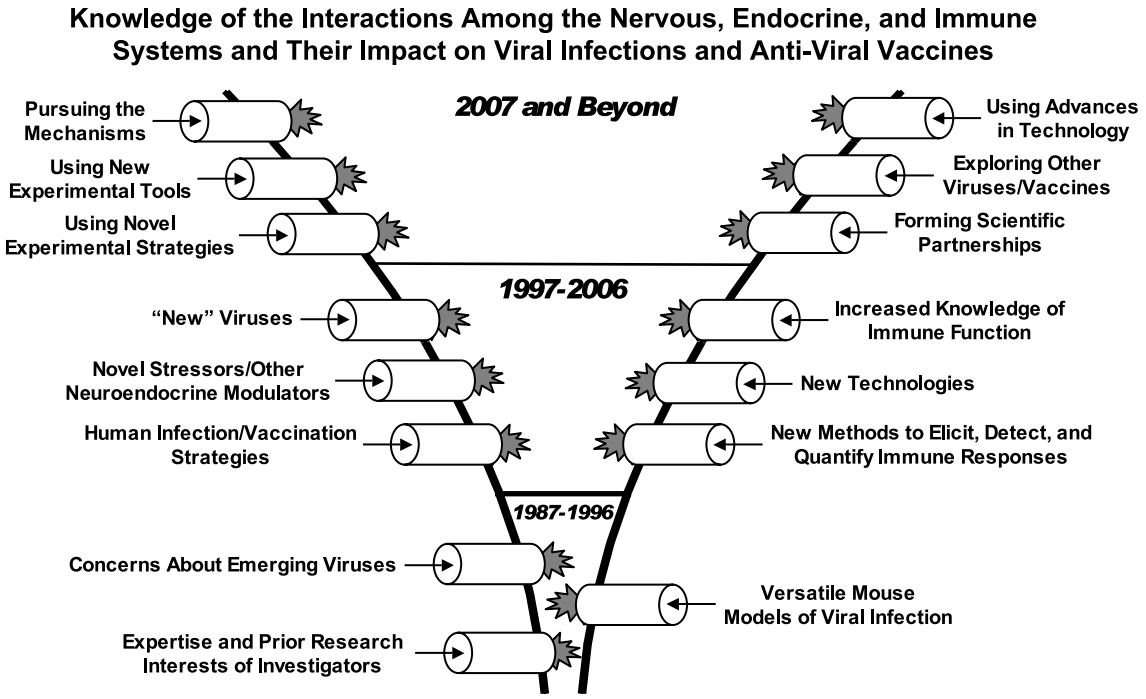

Fig. 1. Knowledge of the interactions among the nervous, endocrine, and immune systems and their impact on viral infections and anti-viral vaccines. A number of factors have and will continue to increase our understanding of the impact of the interactions among the nervous, endocrine, and immune systems and the ability of these interactions to modulate viral pathogenesis.

of these established investigators, as well as newcomers to the field of psychoneuroimmunology, will address this challenge by forming scientific partnerships at the local, national, and international levels. Such partnerships are needed to foster the development of novel experimental strategies to delineate the intricate interactions among the nervous, endocrine, and immune systems. One can only imagine the technological advances that will be developed in the future and how these advances will be instrumental in propelling our knowledge of psychoneuroimmunology to even higher levels. Such efforts will obviously provide a foundation for future publications in *Brain, Behavior, and Immunity*.

4.3. Psychoneuroimmunology—on the right pathway

In 2002, a series of meetings was convened by the National Institutes of Health to chart a "roadmap" for medical research in the 21st century. The purpose of these meetings was to identify major opportunities and gaps in biomedical research that no single institute at NIH could tackle alone but that the agency as a whole must address to make the biggest impact on the progress of medical research. This roadmap, which will be periodically refined by nationally recognized leaders across academia, industry, government, and the public, outlines the priorities of NIH to optimize its research endeavors.

One of the major objectives outlined in the NIH Roadmap is the development of initiatives to encourage scientists to forge new and more advanced disciplines from existing ones. In other words, these objectives seek to promote and foster the development of interdisciplinary research. Simply put, interdisciplinary research integrates the analytical strengths of two or more often disparate scientific disciplines to create a new hybrid discipline. Psychoneuroimmunology is an excellent example of such a hybrid discipline. Clearly, the field of psychoneuroimmunology has already utilized this integration of disciplines for more than three decades through the merging of fields such as endocrinology, immunology, neuroscience, pharmacology, physiology, psychiatry, psychology, to name but a few. Even within these individual disciplines it has been difficult to define conceptual and functional boundaries. The addition of infection by pathogenic microorganisms to this medley of disciplines affixes another level of complexity to the many difficult equations that psychoneuroimmunologists are attempting to solve. A growing understanding of the intricacies of such pathogens, and the development of new methodologies to measure immune responses to infection by these pathogens has further promoted their inclusion in psychoneuroimmunology-related studies.

Despite engaging seemingly unrelated disciplines, the traditional gaps in terminology, experimental approach, and methodology may be eliminated as the number of researchers engaged in interdisciplinary studies grows. Reduction of potential roadblocks will broaden the scope of investigation into biomedical problems and yield new and possibly unexpected results. This approach to research will be transformative and is likely to give rise to new "inter-disciplines" that are more analytically sophisticated. *Brain, Behavior, and Immunity* will play a significant role in disseminating research findings that provide a qualitative and quantitative understanding of the many interconnected networks of molecules that comprise and regulate the function our cells, tissues, organs, and organ systems. This journal, in the coming years, can also provide a venue for promoting the translation of this understanding into effective prevention strategies and new treatment regimens to improve human health.

4.4. Brain, behavior, and immunity—extending the pathway

Research articles appearing in future volumes of *Brain, Behavior, and Immunity* will build on the knowledge base that exists and will provide data that will help to continue to unravel the mechanisms through which mind–body interactions influence the immune system. Technological advances in imaging (e.g., MRI, fMRI, and PET), the completion of the sequencing of the human genome, and the rapid development of proteomics, will provide opportunities to further investigate the mind–body relationship. The advances driven by new technologies will help fit together the many pieces that comprise the puzzle known as psychoneuroimmunology, and this in turn may lead to the development of new and more effective treatments and interventions designed to improve human health.

Future publications in *Brain, Behavior, and Immunity* may be able to capitalize on the human genome sequence. By scanning a genome sequence, gene probes could reveal which genes and protein products participate in specific brain or immune functions and reveal an intimate influence of stress upon their expression. Other variables that have received little attention but that may contribute to the neuroendocrine–immune-pathogen relationships include aging, gender, and metabolic diseases such as diabetes.

In summary, *Brain, Behavior, and Immunity* has established itself as the primary platform to disseminate scientific information regarding the interactions among the nervous, endocrine, and immune systems and their relevance to viral infection. Future studies of these interactions will likely follow the NIH Roadmap initiatives for promoting interdisciplinary research and will take advantage of state-of-the-art technologies developed in each of the disciplines that comprise research in psychoneuroimmunology.

References

Ader, R. (Ed.), 1981. Psychoneuroimmunology, first ed. Academic Press, New York.

Ader, R. (Ed.), 2007. Psychoneuroimmunology, fourth ed. Academic Press, San Diego.

Ader, R., Felten, D.L., Cohen, N. (Eds.), 1991. Psychoneuroimmunology, second ed. Academic Press, San Diego.

Ader, R., Felten, D.L., Cohen, N. (Eds.), 2001. Psychoneuroimmunology, third ed. Academic Press, San Diego.

Avitsur, R., Hunzeker, J., Sheridan, J.F., 2006. Role of early stress in the individual differences in host response to viral infection. Brain Behav. Immun. 20, 339–348.

Bonneau, R.H., 1996. Stress-induced effects on integral immune components involved in herpes simplex virus (HSV)-specific memory cytotoxic T lymphocyte activation. Brain Behav. Immun. 10, 139–163.

Bonneau, R.H., Sheridan, J.F., Feng, N.G., Glaser, R., 1991a. Stress-induced effects on cell-mediated innate and adaptive memory components of the murine immune response to herpes simplex virus infection. Brain Behav. Immun. 5 (3), 274–295.

Bonneau, R.H., Sheridan, J.F., Feng, N.G., Glaser, R., 1991b. Stress-induced suppression of herpes simplex virus (HSV)-specific cytotoxic T lymphocyte and natural killer cell activity and enhancement of acute pathogenesis following local HSV infection. Brain Behav. Immun. 5 (2), 170–192.

Brenner, G.J., Moynihan, J.A., 1997. Stressor-induced alterations in immune response and viral clearance following infection with herpes simplex virus-type 1 in BALB/c and C57B1/6 mice. Brain Behav. Immun. 11 (1), 9–23.

Campbell, T., Meagher, M.W., Sieve, A., Scott, B., Storts, R., Welsh, T.H., Welsh, C.J., 2001. The effects of restraint stress on the neuropathogenesis of Theiler's virus infection: I. Acute disease. Brain Behav. Immun. 15 (3), 235–254.

Capitanio, J.P., Mendoza, S.P., Baroncelli, S., 1999. The relationship of personality dimensions in adult male rhesus macaques to progression of simian immunodeficiency virus disease. Brain Behav. Immun. 13 (2), 138–154.

Carpenter, G.W., Garza Jr., H.H., Gebhardt, B.M., Carr, D.J., 1994. Chronic morphine treatment suppresses CTL-mediated cytolysis, granulation, and cAMP responses to alloantigen. Brain Behav. Immun. 8 (3), 185–203.

Doyle, W.J., Gentile, D.A., Cohen, S., 2006. Emotional style, nasal cytokines, and illness expression after experimental rhinovirus exposure. Brain Behav. Immun. 20 (2), 175–181.

Dunn, A.J., Powell, M.L., Moreshead, M.V., Gaskin, J.M., Hall, N.R., 1987. Effects on Newcastle disease virus administration to mice on the metabolism of cerebral biogenic amines, plasma corticosterone, and lymphocyte proliferation. Brain Behav. Immun. 1 (3), 216–230.

Edwards, K.M., Burns, V.E., Reynolds, T., Carroll, D., Drayson, M., Ring, C., 2006. Acute stress exposure prior to influenza vaccination enhances antibody response in women. Brain Behav. Immun. 20 (2), 159–168.

Feng, N., Pagniano, R., Tovar, C.A., Bonneau, R.H., Glaser, R., Sheridan, J.F., 1991. The effect of restraint stress on the kinetics, magnitude, and isotype of the humoral immune response to influenza virus infection. Brain Behav. Immun. 5, 370–382.

Fisher, S.N., Vanguri, P., Shin, H.S., Shin, M.L., 1995. Regulatory mechanisms of MuRantes and CRG-2 chemokine gene induction in central nervous system glial cells by virus. Brain Behav. Immun. 9, 331–344.

Glaser, R., Friedman, S.B., Smyth, J., Ader, R., Bijur, P., Brunell, P., Cohen, N., Krilov, L.R., Lifrak, S.T., Stone, A., Toffler, P., 1999. The differential impact of training stress and final examination stress on herpesvirus latency at the United States Military Academy at West Point. Brain Behav. Immun. 13, 240–251.

Glaser, R., Padgett, D.A., Litsky, M.L., Baiocchi, R.A., Yang, E.V., Chen, M., Yeh, P.E., Kilmas, N.G., Marshall, G.D., Whiteside, T., Herberman, R., Kiecolt-Glaser, J., Williams, M.V., 2005. Stress-associated changes in the steady-state expression of latent Epstein–Barr virus: implications for chronic fatigue syndrome and cancer. Brain Behav. Immun. 19, 91–103.

Glaser, R., Pearson, G.R., Jones, J.F., Hillhouse, J., Kennedy, S., Mao, H.Y., Kiecolt-Glaser, J.K., 1991. Stress-related activation of Epstein–Barr virus. Brain Behav. Immun. 5, 219–232.

Glaser, R., Rice, J., Sheridan, J., Fertel, R., Stout, J., Speicher, C., Pinsky, D., Kotur, M., Post, A., Beck, M., et al., 1987. Stress-related immune suppression: health implications. Brain Behav. Immun. 1, 7–20.

Hinson, E.R., Hannah, M.F., Norris, D.E., Glass, G.E., Klein, S.L., 2006. Social status does not predict responses to Seoul virus infection or reproductive success among male Norway rats. Brain Behav. Immun. 20, 182–190.

Hunzeker, J., Padgett, D.A., Sheridan, P.A., Dhabhar, F.S., Sheridan, J.F., 2004. Modulation of natural killer cell activity by restraint stress during an influenza A/PR8 infection in mice. Brain Behav. Immun. 18, 526–535.

Karp, J.D., Moynihan, J.A., Ader, R., 1997. Psychological influences on immune responses to HSV-1 infection in BALB/c mice. Brain Behav. Immun. 11, 47–62.

Kelley, S.P., Moynihan, J.A., Stevens, S.Y., Grota, L.J., Felten, D.L., 2002. Chemical sympathectomy has no effect on the severity of murine AIDS: murine AIDS alone depletes norepinephrine levels in infected spleen. Brain Behav. Immun. 16, 118–139.

Kiecolt-Glaser, J.K., Glaser, R., Gravenstein, S., Malarkey, W.B., Sheridan, J., 1996. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc. Natl. Acad. Sci. USA 93, 3043–3047.

Klein, S.L., Marson, A.L., Scott, A.L., Ketner, G., Glass, G.E., 2002. Neonatal sex steroids affect responses to Seoul virus infection in male but not female Norway rats. Brain Behav. Immun. 16, 736–746.

Kohut, M.L., Martin, A.E., Senchina, D.S., Lee, W., 2005. Glucocorticoids produced during exercise may be necessary for optimal virus-induced IL-2 and cell proliferation whereas both catecholamines and glucocorticoids may be required for adequate immune defense to viral infection. Brain Behav. Immun. 19, 423–435.

Lewandowski, G., 1997. Immunohistochemical examination of intracerebral T cell recruitment and adhesion molecule induction in herpes simplex virus-infected mice. Brain Behav. Immun. 11, 264–272.

Lowder, T., Padgett, D.A., Woods, J.A., 2005. Moderate exercise protects mice from death due to influenza virus. Brain Behav. Immun. 19, 377–380.

Marshall Jr., G.D., Agarwal, S.K., Lloyd, C., Cohen, L., Henninger, E.M., Morris, G.J., 1998. Cytokine dysregulation associated with exam stress in healthy medical students. Brain Behav. Immun. 12, 297–307.

Marsland, A.L., Cohen, S., Rabin, B.S., Manuck, S.B., 2006. Trait positive affect and antibody response to hepatitis B vaccination. Brain Behav. Immun. 20, 261–269.

Nair, M.P., Schwartz, S.A., 1995. Synergistic effect of cortisol and HIV-1 envelope peptide on the NK activities of normal lymphocytes. Brain Behav. Immun. 9, 20–30.

Ortiz, G.C., Sheridan, J.F., Marucha, P.T., 2003. Stress-induced changes in pathophysiology and interferon gene expression during primary HSV-1 infection. Brain Behav. Immun. 17, 329–338.

Phillips, A.C., Burns, V.E., Carroll, D., Ring, C., Drayson, M., 2005. The association between life events, social support, and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults. Brain Behav. Immun. 19, 325–333.

Phillips, A.C., Carrolla, D., Burns, V.E., Ring, C., Macleod, J., Drayson, M., 2006. Bereavement and marriage are associated with antibody response to influenza vaccination in the elderly. Brain Behav. Immun. 20, 279–289.

Pierson, D.L., Stowe, R.P., Phillips, T.M., Lugg, D.J., Mehta, S.K., 2005. Epstein–Barr virus shedding by astronauts during space flight. Brain Behav. Immun. 19, 235–242.

Pollack, H., Kuchuk, A., Cowan, L., Hacimamutoglu, S., Glasberg, H., David, R., Kresinski, K., Borkowsky, W., Oberfield, S., 1996. Neurodevelopment, growth, and viral load in HIV-infected infants. Brain Behav. Immun. 10, 298–312.

Raison, C.L., Broadwell, S.D., Borisov, A.S., Manatunga, A.K., Capuron, L., Woolwine, B.J., Jacobson, I.M., Nemeroff, C.B., Miller, A.H., 2005. Depressive symptoms and viral clearance in patients receiving interferon-alpha and ribavirin for hepatitis C. Brain Behav. Immun. 19, 23–27.

Swiergiel, A.H., Dunn, A.J., 1999. The roles of IL-1, IL-6, and TNFalpha in the feeding responses to endotoxin and influenza virus infection in mice. Brain Behav. Immun. 13, 252–265.

Toth, L.A., Hughes, L.F., 2004. Macrophage participation in influenza-induced sleep enhancement in C57BL/6J mice. Brain Behav. Immun. 18, 375–389.

Traynor, T.R., Majde, J.A., Bohnet, S.G., Krueger, J.M., 2006. Sleep and body temperature responses in an acute viral infection model are altered in interferon type I receptor-deficient mice. Brain Behav. Immun. 20, 290–299.

Tseng, R.J., Padgett, D.A., Dhabhar, F.S., Engler, H., Sheridan, J.F., 2005. Stress-induced modulation of NK activity during influenza viral infection: role of glucocorticoids and opioids. Brain Behav. Immun. 19, 153–164.

Vitkovic, L., Chatham, J.J., da Cunha, A., 1995. Distinct expressions of three cytokines by IL-1 stimulated astrocytes in vitro and in AIDS brain. Brain Behav. Immun. 9, 378–388.

Welsh, C.J., Bustamante, L., Nayak, M., Welsh, T.H., Dean, D.D., Meagher, M.W., 2004. The effects of restraint stress on the neuropathogenesis of Theiler's virus infection II: NK cell function and cytokine levels in acute disease. Brain Behav. Immun. 18, 166–174.

Wonnacott, K.M., Bonneau, R.H., 2002. The effects of stress on memory cytotoxic T lymphocyte-mediated protection against herpes simplex virus infection at mucosal sites. Brain Behav. Immun. 16, 104–117.

Yorty, J.L., Bonneau, R.H., 2004. Prenatal transfer of low amounts of herpes simplex virus (HSV)-specific antibody protects newborn mice against HSV infection during acute maternal stress. Brain Behav. Immun. 18, 15–23.