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A global view of twenty years of *Brain, Behavior, and Immunity*

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To mark the 20th anniversary of the publication of *Brain, Behavior, and Immunity (BBI)*, the current editors have arranged for a yearlong series of historical papers on research areas that have matured during the past 20 years. The papers will be written by investigators who were and continue to be active in the field of psychoneuroimmunology. This will be the second Named Series in the journal and is entitled, "Twenty Years of *Brain, Behavior, and Immunity*." Dr. Eric Smith at the University of Texas Medical Branch in Galveston will serve as Guest Editor of this Named Series. Dr. Smith and colleagues were at the cutting edge of psychoneuroimmunology in 1987, and his active research program continues today. As the current President of the PsychoNeuroImmunology Research Society, Dr. Smith is ideally positioned to guide this series to successful completion. In some ways, this brief commentary is an analogous statement on the maturation of *BBI*. Psychoneuroimmunology has, in the past 20 years, passed through stages of greater and then lesser opposition. The field has now reached the point where, if it is not totally accepted as being self evident, it is a *bonafide* specialized area of interdisciplinary research characterized by societies, journals, books, international meetings and NIH research grants. These are the trappings of a viable and important scientific enterprise.

As originally envisioned, the goal of *BBI* was (and still is) to provide a vehicle for publication of the results of scientifically rigorous research on brain, behavior, and immune system interactions. The main components are the role of the brain and behavior in modulating immunity and the role of immune processes in the regulation of neural and endocrine functions and behavior. The raison d'être for *BBI* was given in the opening editorial in the inaugural issue of the Journal. And if we paraphrase passages from that earlier editorial, it is because the issues are as relevant today as they were in 1987 and because we sometimes need to be reminded of where we came from.

Both the nervous and immune systems evolved with an exquisite capacity to receive, interpret, and respond to specific forms of stimulation originating from the external or internal milieu while appearing to be relatively insensitive to other sources of information. As a result, the neurosciences and immunology developed and matured without seriously considering the possibility that there might be channels of communication between these systems that could mutually influence their respective functions. It should be remembered that "physiology," in the sense in which it was used by Claude Bernard, depends upon regulatory interactions among different organ systems to maintain a constant internal milieu. For example, the heart must communicate and interact with the kidney so as to maintain blood pressure that provides tissue oxygenation during vastly different environmental demands. In the same manner, the endocrine system communicates with the brain, a field that has long been defined as neuroendocrinology,

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and extended to psychoneuroendocrinology. Likewise, the immune system communicates with the brain. *BBI* has been a leading journal in publishing data that have defined the broad pathways of reciprocal communication systems between the brain and the immune system.

We have been identifying the efferent and afferent pathways underlying neuroimmune interactions. It is now known that primary and secondary lymphoid tissues are sympathetically innervated, and that the stimulation or interruption of these connections influence immune functions; receptors on lymphocytes are capable of receiving signals emanating from neural and endocrine activity; and, the brain is capable of detecting signals released by an activated immune system. More recently, it has been recognized that cells of the innate immune system in the nervous system, such as microglia, are intimate players in these pathways. Indeed, we are no longer primarily concerned with questions about whether leukocytes express receptors for neurotransmitters, or whether cells in the nervous system express receptors for cytokines. Major issues that are now being addressed include the identification of all the channels of communication between the brain and the immune system and the nature, magnitude and extent of the effects enabled by these pathways. Scientists in psychoneuroimmunology are now defining the conditions under which and the mechanisms by which such brain–immune system interactions take place and how disturbances in these systems contribute to our understanding of the pathophysiology of both immune and nervous systems disorders, how these interactions are involved in critical periods of development and how they affect quality of life for both the young and the elderly.

With the wisdom of hindsight, it would be amazing indeed if homeostasis could be maintained in challenging environments without immune to brain communication, and vice versa. How could we have been so blind just 20 years ago? Today, psychoneuroimmunology is accepted as a new hybrid discipline and a vital field of interdisciplinary research. There is no subspeciality of biomedical sciences that has not been invaded by psychoneuroimmunology. Who would have thought that psychoneuroimmunology is involved in type II diabetes or cardiovascular disease, or that proinflammatory cytokines are now recognized as players in mental health?

Given the communication pathways between the brain and the immune system that already have been identified, it is hardly surprising that immunological states would have consequences for behavior and its emotional components that would be capable of influencing immune functions. Based on what we have learned thus far, the early proposition that changes in immune function might mediate the effects of psychosocial factors and stress on the susceptibility to and/or the precipitation or progression of some diseases and mental health processes has become an increasingly viable hypothesis. Studies in animals and in humans provide evidence that affective responses to what are perceived to be stressful life experiences are accompanied by autonomic and neuroendocrine changes capable of influencing immune function which could, presumably, influence susceptibility to infectious, autoimmune, and neoplastic diseases. On the other hand, behavioral interventions that reduce anxiety or distress decrease the intensity or duration of autonomic and neuroendocrine responses and are presumed to effect changes in immune function that promote wellness and/or recovery from disease. At the present time, we know considerably more about the former than the latter.

It is appropriate to recognize the need to document the clinical significance of behaviorally induced alterations in immune function. However, the rush to influence disease susceptibility by applying neuroendocrine or behavioral interventions, the immunologic effects of which have not been adequately defined, may be premature. As we sharpen our tools, and as the nature of the basic relationships among behavioral, neural, endocrine, and immune processes become clearer, questions about clinical relevance will be addressed with increasing sophistication and are likely to appear with increasing frequency in the pages of *BBI*.

For those readers who may be unfamiliar with *BBI* or the PsychoNeuroImmunology Research Society, psychoneuroimmunology is most succinctly defined as the study of brain–immune system interactions. That is, psychoneuroimmunology addresses the integrated nature of the relationships among behavioral, neural, endocrine, and immune responses that enable an organism to adapt to the environment in which it lives. This is what medical schools used to call systemic physiology. This theme of disciplinary integration is now being endorsed by the National Institutes of Health. The NIH Roadmap, a description of new *trans*-NIH initiatives, argues that, "Biomedical research traditionally has been organized…into broad areas of scientific interest and then [grouped] into distinct, departmentally based specialties. But, as science has advanced over the past decade… two fundamental themes are apparent: the study of human biology and behavior is a wonderfully dynamic process, and the traditional divisions within biomedical research may in some instances impede the pace of scientific discovery. To lower these artificial organizational barriers, the NIH will implement several initiatives designed to facilitate interdisciplinary research collaborations and research training and, ultimately, lead to the development of new hybrid disciplines that will provide a more complete understanding of psychological, social and biological interactions in health and disease." Psychoneuroimmunology is one such hybrid discipline and *BBI* is a vehicle for the expression of such interdisciplinary research. Both should prosper under these NIH initiatives.

Brain, Behavior, and Immunity was launched 20 years ago in large part because established journals, particularly in the field of immunology, were not especially receptive to studies on behavior–neuroendocrine–immune system interactions. In its first 20 years, however, *BBI* has grown from publishing 30–40 papers in four issues per year to publishing 60–70 articles in six issues per year. The latest figures available from the Institute for Scientific Information (2005) show *BBI* with an impact factor score of 3.520, placing it within the top 30% of 115 immunology journals, the top 30% of 200 neuroscience journals, and in the top 20% of all psychology and behavioral science journals. For that performance, we thank our readership and, especially, the scientists who have been submitting and publishing their work in *BBI*.

With its integrative philosophy, *BBI* has served and will continue to serve to broaden the perspective and extend the boundaries of the behavioral and neural sciences and of immunology. Psychoneuroimmunology has spawned the birth of an entirely new generation of scientists who study the brain, behavior and immunology as a coordinated biological defense system, and *BBI* has become the primary vehicle for the dissemination of these new observations. We believe that the most important information to be derived from such interdisciplinary research is a greater understanding of the adaptive functions of brain–behavior–immune system interactions and their implications for the definition or redefinition and for the treatment of a variety of disease processes