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Psychosocial influences on immunity, including effects on immune maturation and senescence

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Abstract

Studies investigating the influence of psychosocial factors on immunity played a critical and formative role in the field of psychoneuroimmunology (PNI), and have been a major component of articles published in Brain, Behavior and Immunity (BBI). An analysis of papers during the first two decades of BBI from 1987–2006 revealed three behavior-related topics were most prominent: 1) stress-induced changes in immune responses, 2) immune correlates of psychopathology and personality, and 3) behavioral conditioning of immunity. Important subthemes included the effect of early rearing conditions on immune maturation in the developing infant and, subsequently, psychosocial influences affecting the decline of immunity in the senescent host. The responsiveness of cell functioning in the young and elderly helped to validate the view that our immune competence is malleable. Many technical advances in immune methods were also evident. Initially, there was a greater reliance on *in vitro* proliferative and cytolytic assays, while later studies were more likely to use cell subset enumerations, cytokine quantification, and indices of latent virus reactivation. The reach of PNI extended from the traditional clinical entities of infection, autoimmunity, and cancer to attain a broader relevance to inflammatory physiology, and thus to asthma, cardiovascular and gastrointestinal disease. There continue to be many theoretical and applied ramifications of these seminal findings. Fortunately, the initial controversies about whether psychological processes could really impinge upon and modify immune responses have now receded into the pages of history under the weight of the empirical evidence.

1. Introduction

Although the P aspects of the PNI acronym for psychoneuroimmunology were a critical driving force that led up to the coalescence of this scientific field, they were once considered to be the most controversial component. The early and sometimes intense debates about the significance of the P domain have subsided but lingering feelings still resurface occasionally in discussions about whether the field's name should have emphasized just the physiological aspects of the brain-immune relationship, with a more circumscribed term, such as '*neuroimmunomodulation*'. The primary issue of concern several decades ago was whether immunologists, as well as some clinicians, might respond skeptically to the once less substantiated claim that psychological processes can meaningfully affect immune processes to such a degree that they undermine health or exacerbate the pathophysiology of disease. For

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many, then and now, this intellectual tension was unwarranted because it had already been established that psychological processes can significantly alter the activity of the same neural and endocrine pathways that were more readily accepted as being able to modify immune responses.

The boundary lines for the possible P factors that affect immune responses have never been explicitly drawn. However, they certainly encompass the influence of psychosocial processes, such as personality and psychopathology, on immunity. Environmental and behavioral factors that sufficiently challenge psychological wellbeing to simultaneously exert immune-modulating effects are also usually included. Much of the latter research has been concerned with the changes in immune responses that occur after stressful or traumatic events. For example, the alterations in the number and types of leukocytes in the blood stream or stress-induced reductions in the levels of antibody generated following immunization. Perhaps as importantly, researchers investigating these psychological influences have also had an abiding interest in those factors that buffer the individual against adversity and thereby lessen or prevent the negative immune changes from occurring. More recently, there have been a number of articles advocating positive and salubrious influences that might actually enhance physical wellbeing, perhaps by stimulating or sustaining some aspects of immunity (Marsland et al., 2006). For example, PNI research has contributed to a growing literature on '*successful aging*': the view that our life style and outlook enable us to postpone what was once thought to be the inevitable and strictly biological process accounting for physical decline and immune senescence at the end of the life span.

The primary aim of this short review is to trace some of the historical trends since the journal BBI came into existence, and to highlight landmark studies that helped to advance and refine our thinking about the psychological aspects of PNI. Following the expository style and outlines employed by other reviews in this series, we begin with the knowledge extant in the early 1980s and then progress sequentially in two incremental steps through the periods from 1987-to-1996 and from 1997-to-2006. In embarking on this journey, it goes without saying that there were many who made pioneering contributions before the decade of our embarkation and that page constraints necessitate a delimited summary. Numerous important papers could not be cited in a selective review, and other authors could certainly argue that the unmentioned discoveries were just as pivotal to the field's progress.

In reconstructing the past, historians must tread warily on the dimly lit and shrouded ground, because they bring their own perceptions to the task, and introduce the inevitable bias of looking back from today's vantage point. Not all of the promising avenues and lines of inquiry from the early days of PNI were pursued with equal vigor, in part because funding priorities soon constrained the initial diversity and helped to select which topics rose to greater prominence. Especially in the mid-1980s, the urgency to learn more about factors that might influence viral infection and the progression of AIDS was key in guiding the types of PNI research supported by the NIMH, the primary source of funding for psychological studies at that time. In particular, there was considerable interest in the protective benefits of social support and how stress or certain personality attributes might affect survival. The immune correlates of depression continued to be an area of active investigation over time (Zorilla et al., 2001; see also 2002 Special Issue on "Cytokines and Depression", 16:5), whereas research on the immune dysfunction associated with schizophrenia has waned (notwithstanding the provocative findings summarized in the 2001 Special Issue on the "Immunobiology of Serious Psychiatric Diseases", 15:4). There would also be a growth of interest in the hormone and immune correlates of posttraumatic stress disorder (PTSD), a topic barely on the horizon in early days of PNI research (Laudenslager et al., 1998; Yehuda, 2003).

2. Pre-1987

An examination of the publications and state of knowledge in the early 1980s reveals an overarching framework not too dissimilar from views prevailing today. Figure 1 illustrates the perspective advocated by Cunningham (1981), an immunologist interested in PNI, in which he envisioned the immune system as subject to influences by the brain (mind) and its many interactions with the body's other physiological systems. In turn, these complex and reciprocally linked biological processes within the individual were seen as being embedded within a larger context: a set of relationships that connect us to our social networks and to the physical world. While this theoretical model is hardly controversial today, writers at the time felt the evidence supporting this perspective was sufficiently tenuous that they were compelled to advocate for it by providing documented examples showing that our immune responses could be as strongly influenced by mind/body relationships as by trauma or physical challenge.

Investigators engaged in considerable effort to discern how these cognitive and/or emotional effects might be transmitted down to the cellular level. The papers typically described experiments showing that immune alterations could be induced by stress and/or correlated with parallel changes in the brain or endocrine system. Increased hormone secretion by the hypothalamic-pituitary-adrenal axis and elevated activity in the sympathetic nervous system proved to be important conduits to the immune system. Researchers speculated about the many other possible mediators, but few could have anticipated measuring the full complement of pathways assessed today: from the many inflammatory and regulatory cytokines to the myriad number of proteins responsible for angiogenesis and cell growth.

Review articles from this time period frequently relied on epidemiological evidence to support the claim that psychological factors were associated with illness. It was argued that some personality attributes, such as a person's inability to express emotion, could affect cancer or AIDS progression, increase morbidity and hasten mortality. Often recurrent in these formative writings were reflections on an earlier, more speculative era of psychosomatic medicine, when some thought that cognitive and emotional processes could really '*get under the skin*' and become manifest as specific clinical conditions (Solomon & Moos, 1964). This belief in a specific typology from the heyday of psychoanalysis, with psychic and emotional energy becoming manifest as distinct disease entities (e.g., ulcers, asthma, etc), has been largely abandoned. However, elements of those speculative ideas about '*somatization*' still linger in recent theorizing about '*biological embedding*'. Many studies continue to find that experiencing traumatic events early in life can increase the incidence of certain illnesses or predispose for a proinflammatory physiological bias later in adulthood (Danese et al., 2007).

With pressure on PNI researchers to provide concrete proof of significant immune alterations, the preponderance of articles in the first decade were psychological reports of direct effects on immunity, especially documentation of acute immune changes during times of stress and challenge. PNI researchers were cautioned repeatedly that statistically significant changes might not be synonymous with biologically or clinically meaningful effects. Nevertheless, much enthusiasm was generated by the ability to reliably replicate an early finding that bereavement following loss of a spouse resulted in immunosuppression. It was first been evinced by a 2-month long reduction in lymphocyte proliferative responses, but also was extended to include a decrease in NK responses (Bartrop et al.,1977; Irwin et al., 1987). The fact that similar types of immune alterations occurred in depressed patients provided the supportive evidence needed to substantiate the argument that psychological factors really were potent enough to significantly downregulate many immune responses (Andreoli et al., 1993; Irwin, 2002). Grieving and psychiatric depression proved to be just examples of a broader array of evocative states and situations that were potent enough to undermine immune responses.

The list grew to include school examinations, unemployment, and marital discord (Glaser et al., 1987; Kiecolt-Glaser, 1999).

At the same time, the armamentarium of immune measures employed by PNI researchers grew. For example, the analysis of natural killer cell (NK) activity with *in vitro* cytolytic assays gained in popularity. It became clear that the NK cell was among the most responsive of lymphocytes to psychological stimuli. Rapid changes in the number of NK cells in circulation could occur within minutes and significant reductions in lytic activity were sustained for hours and even days-to-weeks after the occurrence of a stressful event (e.g., Kang et al., 1996).

It was already known that an individual's approach to coping with stressful events was fundamental to understanding the extensive variation seen in psychological and physiological reactions. Social relationships, especially the ability to benefit from social support, were considered to be especially important for protecting the individual against perturbations and challenge. The writings of Sheldon Cohen were very influential, especially the dichotomy he proposed between the 'buffering' and 'main effect' models of social support (Cohen & Wills, 1985). The two models distinguished between the protective benefits of social companionship during just the bad times versus the more enduring physiological and health-promoting effects of being socially connected, spanning both the good and bad days.

Similar types of studies on animals substantiated the general conclusions emerging from human research. Experiments on crowding and aggression in rats and mice had already demonstrated that many types of aversive social and housing conditions could impair an animal's immune defenses against infectious pathogens and hamper cellular processes involved in the control of tumor growth (Ben-Eliyahu et al., 1991). Manipulations of the animal's living conditions – especially moving a social species into isolation – were found by many to provoke similar immune changes. Moreover, these results generalized from laboratory rodents to domesticated farm animals, and then received further confirmation in several of the gregarious primate species (Laudenslager et al., 1982). There was now solid evidence that the vigor and effectiveness of immune responses were strongly associated with the physical and social setting in which the animal was living. Just as importantly, many different immune processes could be significantly undermined by emotional disturbance and arousal. Overall, the shifts in immunity appeared to be largely similar whether evoked by disruptions of social relationships, elicited by the unpredictability and arousing features of novel stimuli, or induced by the threatening conditions of electric shock and restraint (Fleshner & Laudenslager, 2004). The association with psychological factors was more than just a rare or difficult-to-discern phenomenon. In fact, there was now ample proof that it was quite commonplace, with both acute and longer-lasting effects of psychological processes on many different immune responses.

3. 1987–1996

Publications in BBI during its inaugural year of 1987 heralded several of the topics that would hold the field's attention and interest for the next 20 years (Fig. 2). The Tables of Contents include titles on the topics of both stress, bereavement and psychopathology (Irwin et al., 1987). Over time these subjects would rival the numbers published on the conditioning of immune responses (Fig. 2). In welcoming authors to submit papers, the founding Editors wrote in the first issue that the all-encompassing title of BBI was intended to be a '*euphonious euphemism for all aspects of the interactions among behavioral, neuroanatomical, neuroendocrine, neurochemical and immune processes*" (1987, 1(1), p. 5). The last issue of that year also contained a short paper on a topic that would be a recurrent subject in the journal: the observation that lasting immune effects could be induced by disturbances of the early rearing environment (Lown & Dutka, 1987;Ackerman et al., 1988).

If disruptions of social relationships and environmental change can affect the immune responses of the adult host, it was certainly reasonable to suspect that a developing individual with an immature and less well-regulated immune system might be even more susceptible. This conclusion had already been reached in a prophetic review written by Robert Ader, the first Editor of BBI (Ader, 1983). He had advocated that not only was the young infant more vulnerable to insults, but that experiences during early rearing could serve an educational role, guiding the normal development of the brain and immune system. However, at that point, the sub-discipline of developmental PNI was still in its infancy. Many studies soon followed, building upon the pioneering observations that the positive stimulation of rat pups by handling and maternal licking, or the occurrence of negative events, such as premature weaning from the mother, could affect antibody responses to antigenic challenge, cellular immune responses, and the capacity to contain a transplanted tumor. Confirmatory evidence for the generality of these conclusions from young rodents was obtained in studies on monkeys when decreases in their lymphocyte proliferative and lytic responses were found to last for 1–2 weeks after separation from the mother or juvenile companions (Laudenslager et al., 1982; for a later review see Coe & Lubach, 2003).

The immune effects induced by the social separation of animals extended to many other cellular responses. However, the studies soon provided some of the earliest evidence that many aspects of innate immunity can be activated by stress. Complement activity, superoxide release by neutrophils and macrophages, and cutaneous hypersensitivity reactions were among the indices stimulated, rather than inhibited, by disturbance in young animals (Coe et al., 1988). By the end of BBI's first decade, the growth of research on developmental PNI would culminate in a special issue devoted entirely to this subject (1996, 10:3). The articles reported on the immune consequences of fetal alcohol exposure as well as the long-term behavioral and physiological effects of neonatal infection and endotoxin exposure. One paper also discussed the immune ramifications of antenatal corticosteroid treatments, a subject still of clinical relevance today for the care of babies born premature (Kavelaars et al., 1996). The subject of environmental influences on the development of the immune system was also revisited in a later special issue on Stress, Genetics and immunity (2006, 20:4), which also focused on the topic of stress and epigenetic programming.

While stress effects on immunity would continue to be a major theme across this 10-year period, rivaling the numbers of papers on neuroscience and hormone-immune interactions (see Fig. 2), the titles reveal some interesting trends. The subject matter of the animal studies broadened to consider immune effects that might occur in more naturalistic settings, including articles showing that pheromones and fear odors can also serve as provocative stimuli for immune change (Cocke et al., 1993;Zalcman et al., 1991). The use of the 'intruder paradigm' gained in popularity as a means to investigate the physiological consequences of natural aggression and social dominance or subordination (Cirulli et al., 1998). At the same time, others continued to employ immune outcome measures as a means to further refine our understanding of the cognitive and perceptual nuances underlying the stressful aspects of novelty and electric shock, two more traditional laboratory paradigms. Several papers were published on the immune changes that occur when rats are confronted with stressful situations with or without '*perceived control'* over the event (Maier & Laudenslager, 1988). Loss of control and unpredictability are potent elicitors of arousal and immune alterations. In contrast, providing information that behavioral responses are effective is helpful for eliminating physiological reactions to the aversive situation. This feedback about the efficacy of responses is also an important aspect of coping, enabling an animal to acclimate and adapt despite the continuance of the challenging or stressful event.

PNI studies with human participants also made many advances during this time period. In particular, assessment of the association between a personal sense of "loneliness' and immunity

provided a dramatic means of showing the significant influence of sociality on immune functioning (reviewed by Kiecolt-Glaser, 1999). Cellular immune responses of lonely students were found to differ from those who were more satisfied with their social relationships. Other research extended these findings on the importance of personality attributes, and demonstrated that an optimistic outlook could be an effective buffer against the immune perturbations induced by negative events. While some of these psychological paradigms would not necessarily have been new for an audience of social scientists, they were employed in unique and creative ways to more definitively link psychosocial variables to immune outcomes. The findings helped to garner more credibility for the field of PNI both at the NIH as well as among the more skeptical community of immunologists. Technical refinements in the ability to immunophenotype lymphocytes also enabled researchers to more specifically quantify changes in the types of leukocytes in circulation, and set the stage for the measurement of activation and adhesion markers. It became easier to discern the effects on cell trafficking and homing, and thereby to provide explanations for the changing cellular responses found with the *in vitro* assays (reviewed later by Dhabhar, 2002).

Simultaneously, there was a growing awareness about the importance of proinflammatory cytokines. Papers in BBI focused primarily interleukin-1 (IL-1) initially, but soon the assessments were broadened to include the triumvirate of IL-1, IL-6 and TNFalpha, as often measured in studies today. Without a doubt, however, one of the most insightful advances had to be the realization that the activation state of latent Herpes viruses could be used to index the host's immune status (Glaser et al., 1991). This programmatic series of studies was certainly a landmark achievement. It demonstrated that many different stressful life events --from school exams to divorce-- elicit a reactivation of Epstein-Barr virus. These findings confirmed earlier, more circumstantial evidence indicating that other types of Herpes viruses, including HSV-1 and 2, can also become activated by stress, but the prior reliance on the expression of symptomatic lesions often yielded more equivocal results. Moreover, the ability to use an increase in antibody titers (accompanying the recrudescence of virus from the latent state) as the outcome measure provided a convincing means to document the considerable physical and emotional cost of being an elderly caregiver for an impaired spouse. Just as a young infant is more susceptible to illness and environmental influences, the immune system of an older individual under challenge reveals its frailty. Their studies convincingly showed that the cellular immune processes that maintain Herpes viruses quiescent were undermined by the psychological distress and demands of being a care provider.

4. 1997–2006

In light of this review's focus on the contributions of psychological research, it is of some historical interest that the first BBI issue in 1997 opened instead with a short commentary entitled "*Where is the "Neuro" in psychoneuroimmunology*?" (Altman, 1997). Summarizing conclusions of a workshop held at the prior PsychoNeuroImmunology Research Society (PNIRS) meeting, the NIMH Program Director for AIDS-related research at that time, highlighted that the latest tools of neuroimaging and neuroelectrophysiology were not often being utilized in the human PNI studies on psychological factors and immunity. While a few BBI papers would subsequently use these techniques, documenting an association between patterns of brain activation and immunity (Wik et al., 1998; Davidson et al., 2001), neuroimaging still is not routinely incorporated into PNI studies to this day.

Nevertheless, there were many other exciting and new approaches during the second decade of BBI that yielded further insights into the important relationships between psychological state, the brain and immune activity, including the seminal work on cytokines and sickness behavior (Dantzer, 2001; Maier, 2003). Cytokines were originally thought to serve primarily as intracellular and paracrine mediators of local immune activity, but research within the

context of PNI demonstrated that cytokines are far more ubiquitous and also facilitate communication across physiological systems. This discovery has to be considered a major galvanizing and historically significant event for the field. In addition to the diverse effects that cytokines have on peripheral body functions, it became clear that they have potent effects in the brain, including on emotional processes and attention and memory functions. Beyond the psychogenic effects induced when cytokines reach high levels in the blood stream -- creating a behavioral state characterized by loss of appetite, malaise, and fatigue – much lower cytokine levels synthesized within the CNS can affect neuroendocrine activity and also act locally in the hippocampus, where they can affect the creation and retrieval of memories. Many deserve credit for these discoveries, but certainly the laboratories of Robert Dantzer, Steve Maier, Linda Watkins, Adrian Dunn, and Hymie Anisman were pivotal in clarifying the important effects of cytokines on behavior and for demonstrating the relevance to many symptoms seen in depression (e.g., Capuron et al., 2002; Maier, 2003). It is also important to note that the pages of BBI included a few articles pointing out that the host can sometimes shrug off these potent cytokine effects when sufficiently motivated (Aubert et al., 1993). The somnolent state induced by the administration of cytokines can be supplanted by the maternal drive to care for young, and the motivation to respond aggressively to an intruder.

During the second decade of BBI, the reach of PNI would also extend further and more credibly into several other clinical arenas. Studies on allergies and asthma continued, with additional demonstrations that stressful life events aggravate the leukocyte biology responsible for inflaming and constricting the airways (Kang et al., 1996). However, the surprising realization that inflammatory processes also contribute to the development of cardiovascular disease may provide an equivalently important pathway whereby stress can affect population health (Black, 2002). This linkage between certain cytokines and the vasculature suggests that when IL-6 levels rise with age, especially in individuals contending with stressful living conditions, they may mediate some of the pathophysiology of atherosclerosis. The research will have thereby helped to delineate some of the processes accounting for the significant disparities in health across different socio-economic strata (Evans et al., 2000). Today, it is difficult to think about the risk factors for metabolic syndrome or heart disease without also considering immune processes and the basic physiology of inflammation (e.g., Mills et al., 1999).

Among the many immune-related physiological processes that can be undermined by stressful psychological events, one more stands out prominently. The research linking negative emotional state to the pace of wound healing is particularly dramatic because of the magnitude of the impairments and the many implications for recovery from trauma and surgery (e.g., Padgett et al., 1998). Microscopic investigations at the site of injury have provided a remarkably, detailed window on the cellular events accounting for these psychological influences on healing. Effects have been observed on the recruitment of cells, cell-to-cell signaling, degree of bacterial infiltration, and rate of new tissue growth.

Psychological factors have also been shown to affect the delicate balance maintained between the mammalian host and its commensal microbiota, most importantly at the mucosal surfaces of the oral cavity and gut (Bailey et al., 2004). This summary is just a partial listing of the many new immune, microbiological, and neuroscience methods that were incorporated in innovative ways into PNI studies (see also Sheridan, 1998). Without a doubt, these technical advances in methodology are among the most impressive achievements during the last decade. Even so, we would be remiss if we didn’t also acknowledge a few other noteworthy accomplishments, including some attained more in the psychosocial realm. PNI has continued to garner increased attention from scholars in other branches of the social sciences. The findings are having an influence on the theorizing by sociologists and economists about population health (Steptoe et al., 2002). Immune-related measures are being employed more often in community studies and even incorporated into larger epidemiological surveys with the goal of explaining associations

between larger societal issues and health. In this context, it should be mentioned that PNI papers continue to document the persistence of immune effects for extended periods of time after environmental disasters and catastrophic weather-related incidents. In addition, characterization of the many long-term hormone and immune ramifications of trauma may help to explain why victims of child maltreatment are often overrepresented in patient populations with gastrointestinal diseases and chronic pain disorders. Similarly, some of the health-related effects of growing up and living in poverty may ultimately prove to be mediated through immune-related pathways. For example, there is the well-established association between growing up in impoverished settings and the increased incidence of allergies and asthma.

With hindsight, we can look back and see that some of these findings were presaged by the research in animals documenting the importance of 'early experiences', in tilting the developmental scale either toward resilience and health or in the direction of illness (Solomon et al., 1968). We have also come to appreciate that these experiential influences can be traced back even earlier to the fetal stage (Weinstock, 2005). As a consequence, these types of findings are used to support arguments in favor of societal policies and programs that promote the benefits of providing higher quality prenatal care. Further research on 'fetal programming' may help us obtain greater insight into the reasons for the worldwide increase in allergies and asthma.

A special BBI issue in 1999 underscored another important theme by focusing on individual differences across people in how psychological factors affect immunity, emphasizing the variation rather than just the differences between groups. The articles discussed the influence of many personality attributes, including optimism, persistent worrying, and social inhibition (Segerstrom et al., 1999), and dared to consider the once controversial idea of personality in animals. Several strains of rats as well as individual animals in the same species of monkey were found to exhibit stable social predispositions and temperaments, which could in turn be associated with distinctive immune profiles. Following infection with simian immunodeficiency virus (SIV), the variation in sociality and behavioral reactivity helped to explain why SAIDS progressed more rapidly in some monkeys (Capitanio et al., 1999). The subject matter of this issue predated a line of inquiry that is popular today – the question of the biological basis of '*neuroendocrine phenotypes*'-- which is likely to include some immune correlates as well.

The fourth issue off BBI in 2001 began with an In Memoriam to Dr. George Solomon, a pioneer in PNI and vocal advocate for its relevance to psychiatry. He liked to mention that he was among the first back in the 1970s to put a sign on his office door proclaiming it a Psychoimmunology Laboratory (his term). The title of Dr. Solomon's autobiography, From Psyche to Soma and Back is probably a good way to remember him and his contributions to the field. The remainder of this issue (15:4) was devoted to the immune correlates of psychopathology, especially schizophrenia, a topic that would have greatly pleased him, even if the underlying mysteries continue to elude us. The last article also reported on an association found between elevated TNF-alpha levels in maternal circulation during pregnancy and the offspring's risk for schizophrenia, which brings us full circle back again to the important relationships between immunity and neurobehavioral processes during early development (Buka et al., 2001).

5. Retrospective and prospective reflections

This historical review of psychologically oriented papers published during the first 2 decades of BBI captures a remarkably productive period spanning several important transitions for the field of PNI. At the outset, the subject of psychological influences on immunity was still

considered controversial by many scientists and clinicians. Twenty years later, the weight of the evidence has now definitively documented that the perspectives of PNI are not only credible, but that immunomodulation by stressors or via behavioral conditioning paradigms, is a reliable and replicable phenomenon. These effects help us to understand the immune alterations associated with psychopathology, especially the inhibition of certain cellular immune responses and the enhancement of some aspects of innate immunity and inflammation. The success of this prodigious effort is evidenced further by the fact that it is far easier to find acceptance for these types of articles beyond BBI in mainstream immunology and clinical journals. It certainly helps to be able to cite a plethora of studies, which have convincingly shown the magnitude of psychological influences on immune competence rivals that of many other extrinsic and intrinsic factors (Fig. 3).

Indeed, perhaps an equally important challenge today is to understand how the immune system filters and distinguishes among these many influences, permitting only the salient and relevant ones to impact functioning. Even more so than when the immune system was viewed as largely autonomous, one has to marvel at its resiliency and ability to protect us against an unending stream of pathogens in the face of so many modulating influences and the unending vicissitudes of day-to-day life. In truth, the immune capabilities of the healthy adult host are remarkably robust. As a consequence, some of the ramifications of the psychologically induced alterations may be of greater clinical concern for the young and elderly or the immune-compromised.

We already have evidence that many important implications of PNI do pertain to a weakened or sick individual. Once compromised by infection or neoplasia, the additional influences of psychological factors now take on added significance. A special BBI issue devoted to psychosocial factors and cancer underscored this relevance of PNI for understanding the etiology and progression of illness (Miller, 2004). It is likely that over the next decade, we will see the translational aspects of PNI become most evident in therapeutic interventions for patient populations, helping to better control disease progression and even to restore the balance needed for a recovery to health.

It is important in this context to pause and reflect on some of the cautionary comments expressed by Nicholas Cohen in his Norman Cousins address entitled "*The uses and abuses of PNI*" (Cohen, 2006). While marveling at the incredible accomplishments of PNI, speaking with the sage voice of an immunologist, he urged us to remain wary of superficial and inflated claims that could undermine the credible achievements. Just as funding pressures influenced the early research agenda in the 1980s, in the future there will be increased pressure to demonstrate the translational relevance of PNI for clinical practice. Current studies investigating the physical and psychological benefits of cognitive-behavioral therapies, meditation, and exercise are thus paving the way to show how PNI principles can be applied in a practical and applied manner to patient care and for health promotion.

Cohen's address also highlighted another point often overlooked because of this emphasis on clinical applications, which is that behavioral influences on immunity are just as likely to be evident in nature as in the laboratory setting or clinic. Arousal, fear, stress, and social competition occur regularly in free ranging populations of animals. We actually know relatively little about the significance of these types of immune effects among natural fauna. For example, it has been shown that social aggression, and the resulting exposure to saliva and blood in the course of biting and wounding, is one means of spreading infectious pathogens between animals, in addition to the viruses conveyed via sexual behavior. It will be of considerable value to more fully incorporate this type of ecologically relevant perspective into the PNI research agenda, especially for some of the newly emerging zoonotic pathogens like avian flu or Hanta virus. It would complement unique insights that have been obtained when evolutionary perspectives were applied to the basic cellular and molecular biology of stress.

For example, the research demonstrating that the physiological reactions to trauma and infection did not originate with mammals. The antecedents can be traced back to the responses of single cells, including the synthesis and release of heat shock proteins.

As highlighted repeatedly in this review, PNI investigators have demonstrated a remarkable ingenuity in how they incorporate innovative methodologies into their research programs. Given the pace at which the field of immunology advances, maintaining this initiative and flexibility to import the latest techniques will be an ongoing challenge. It is an especially demanding regimen for the next generation of PNI researchers, who must simultaneously remain proficient and up-to-date with the prevailing psychological paradigms and current issues in their own disciplines.

While psychologists and psychiatrists tend to focus on the individual, the future will also likely bring us more studies extending beyond the person-oriented analysis to tackle the complex subject of population health. From the outset, the field of PNI attracted researchers who were comfortable with holistic and big perspectives, both with regard to the complicated interactions between physiological systems and with respect to how individuals function within a broader environmental and social context. Larger scale population studies may enable us to test the consequences of policy decisions for public health and help to apply the findings of PNI to improve personal and societal wellbeing. The next retrospective in 20 years will likely report that the PNI research led not only to more discoveries about immunobiology, but also resulted in significant changes in patient care, and illuminated better ways to promote psychological well-being and foster optimal health.

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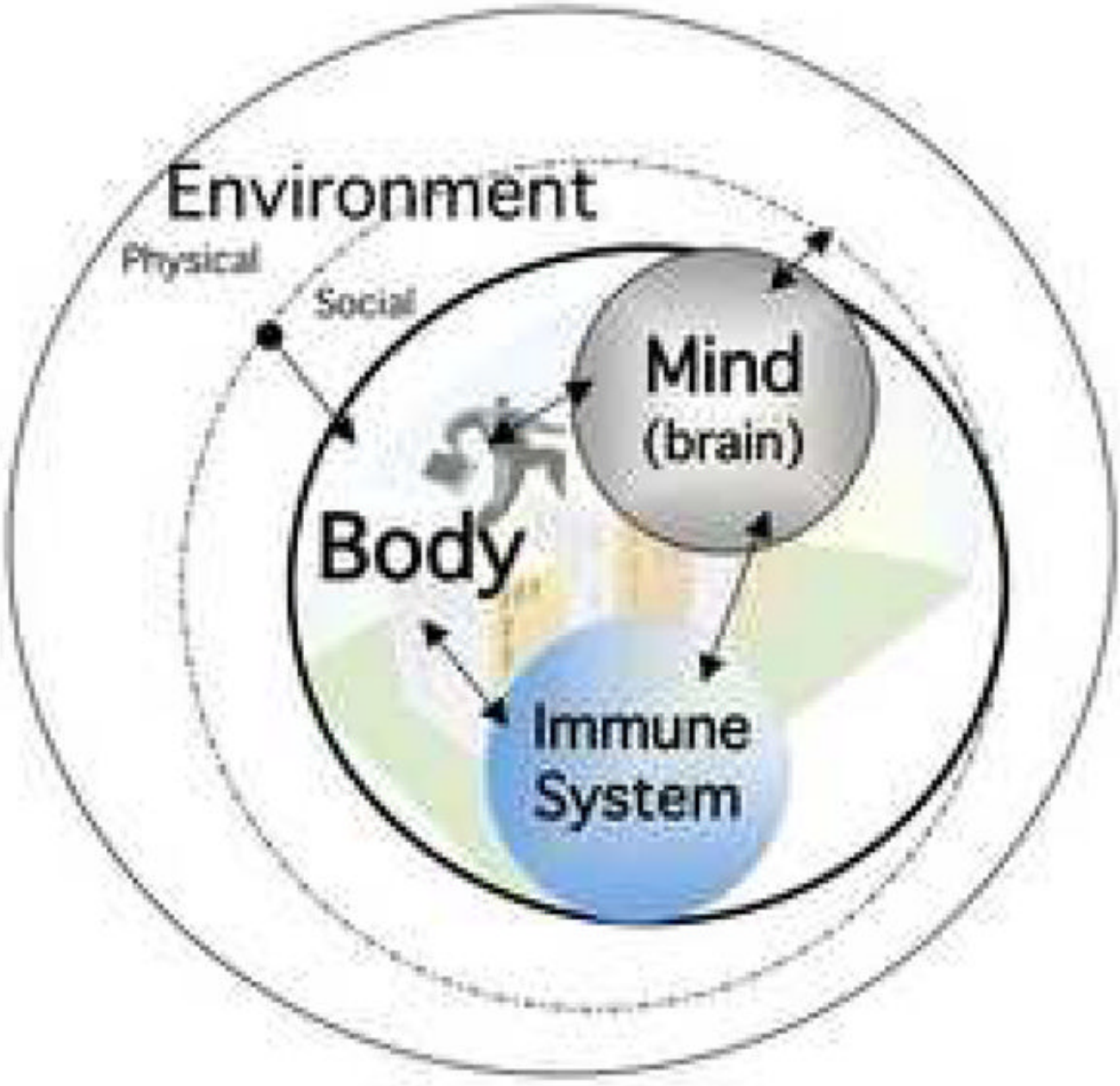

Figure 1.
An early perspective on PNI as envisioned by Cunningham (1981). Artistic rendition of his description of multiple levels of influence on the immune system, first within the body from the brain and other physiological systems. Simultaneously, extrinsic factors impinge upon by the individual, both from the social realm and physical world.

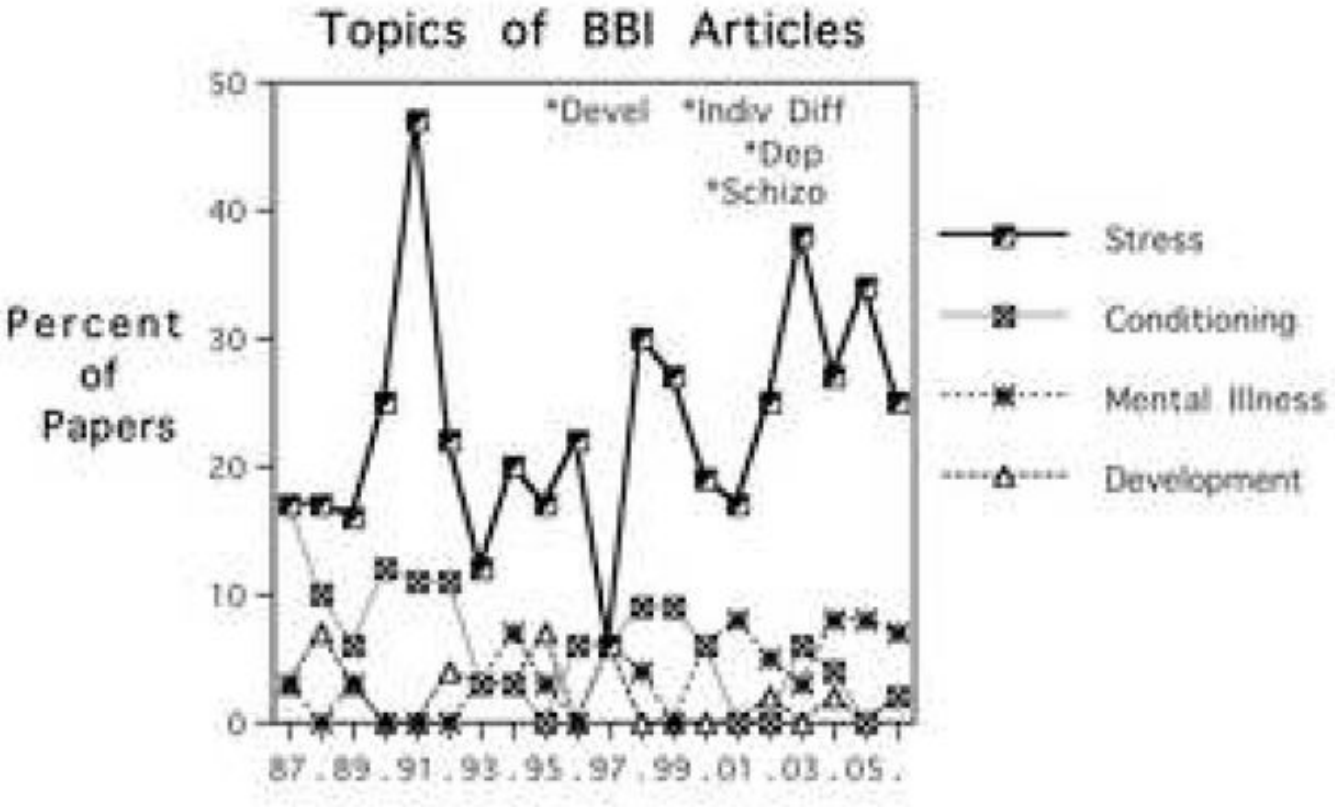

Figure 2.

Historical summary of BBI articles published between 1987–2006, highlighting the number pertaining to psychological influences on immunity. Categorization was based on the main point emphasized in the title. Stress studies rivaled the proportion in the neurosciences (24%), and on hormone-immune interactions (14%) and general immunology (20%). Special issues with a focus on P-related topics were not included; they are designated with an asterisk (*) in the year they were published.

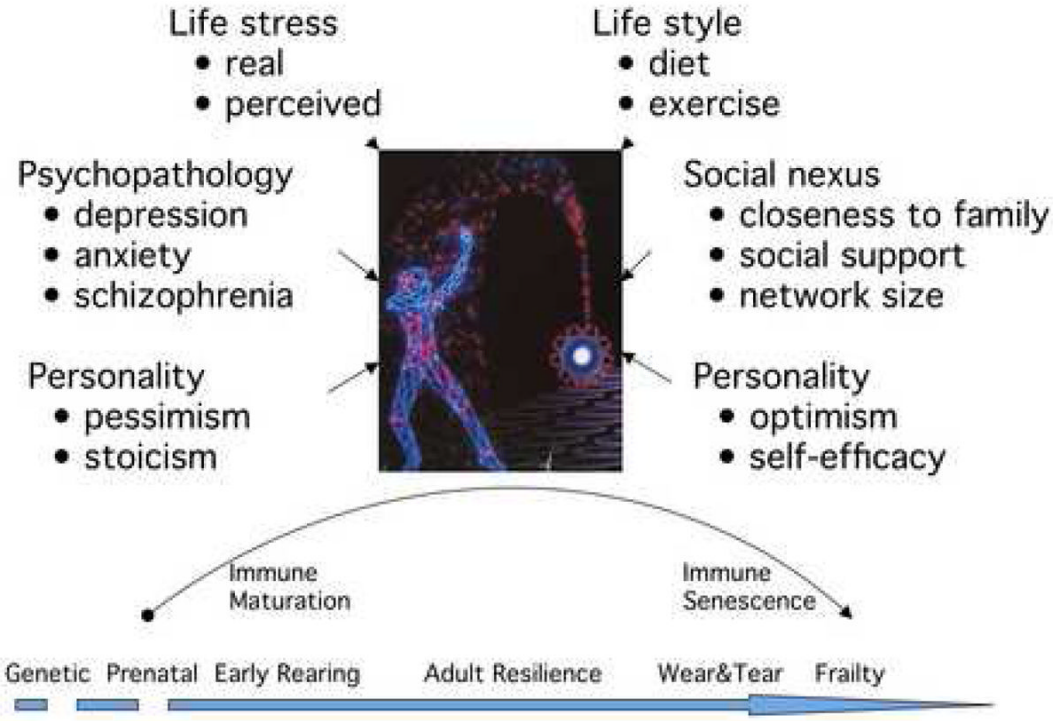

Figure 3.

Illustration of the many types of psychological and behavioral factors that can affect immune competence. Developing and older individuals may be especially susceptible to psychosocial influences because the age-related changes of immune maturation and senescence increase responsiveness and extend the duration of immune effects.