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# The uses and abuses of Psychoneuroimmunology: A global overview

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## Abstract

Studies of interactions between the nervous and immune systems that effect immunological and behavioral changes are relevant to our understanding biological issues pertinent to evolution, ethology, ecology, and aging, in addition to our understanding the immune and nervous systems per se. Psychoneuroimmunology also relates to homeland security, science education, and the practice of conventional as well as complementary and alternative medicine. This paper will highlight just some of these global implications of psychoneuroimmunology. © 2005 Elsevier Inc. All rights reserved.

*Keyword:* Psychoneuroimmunology

## 1. Introductory remarks

To introduce this written version of my 2005 Cousins' address, I will offer some gratuitous advice to the pre- and postdoctoral trainees in the PsychoNeuroImmunology Research Society (PNIRS) who might be wondering what I did to receive our society's Norman Cousins award. I think I received this honor, in part, because I *listened*, I was *curious*, I took a *risk*, and I *proselytized*. I listened to Bob Ader when, in 1974, he came to my office at The University of Rochester Medical Center to talk to me about Pavlovian conditioned taste aversion and the cyclophosphamide (CY)-associated death of some rats. Based on a bit of data that some might consider sketchy, Bob had developed the following hypothesis to explain the aforementioned rat mortality (Ader, 1974). After re-exposing saccharin-CY-conditioned rats to the conditioned stimulus (CS), the CS exposure effected immunosuppression (in addition to taste aversion), thereby increasing vulnerability to unknown environmental pathogens. What struck Bob as provocative was that mortality was not random. Rather, death correlated with the amount of the saccharin CS the rats were given during the single learning trial (Ader, 1974). Condi-

tioning is feed-forward learning and such learning involves higher centers of the central nervous system (CNS). Thus, if one could really condition changes in the immune system, it would mean that the CNS and immune system must be interconnected. After listening to Bob, I was downright intrigued by this possibility that had not been considered by "serious" contemporary immunologists who "knew" that the immune system was "an autonomous agent of defense." To satisfy my curiosity, I accepted Bob's offer to help him directly test his hypothesis by providing the know-how for deliberately immunizing rats (conditioned and not conditioned) and then assaying their serum antibody titers after presentation of the CS.

Why might my early incursion into doing "fun science" now be considered as risk-taking? Those experiments took time, energy, and money from what was my main bread and butter area of NIH-funded research (amphibian immunology/evolutionary immunobiology). Thirty years ago, however, I didn't really think there was a downside to adding another research area to my portfolio. NIH funding was relatively abundant and pursuing uncharted territories was not discouraged by what I believe is the current NIH mentality of only funding applications based on highly focused and targeted research hypotheses that have already been validated by reams of polished "preliminary data."

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The hypothesis that one could condition the immunosuppressive effects of a pharmacologic agent was experimentally supported in 1974 and the results published a year later (Ader and Cohen, 1975). This study, so I've been told, initiated our contemporary understanding that the immune system receives signals from the brain, and the field we now call psychoneuroimmunology. The biological power of such conditioned immunosuppression became obvious a few years later, when we applied similar behavioral conditioning techniques and delayed, by weeks, the progression and mortality associated with the lupus-like disease in (NZB  $\times$  NZW)F<sub>1</sub> mice (Ader and Cohen, 1982). Since these dramatic findings were published in *Science*, they could not help but be seen (and viewed cautiously if not downright skeptically) by card-carrying immunologists.

As a card-carrying immunologist myself, I was invited to talk at various academic institutions about conditioned immunopharmacologic effects. I also chose to speak about this subject rather than the evolution of immunity at national and international immunology meetings. In addition, I contributed a chapter (Cohen and Ader, 1981) about conditioned immunomodulation to a festschrift for Niels Jerne, the Nobel laureate director of the Basel Institute for Immunology, where I had spent a sabbatical year. I concluded that paper by suggesting that in his retirement, Jerne might enjoy modeling these interactions into his network theory of immune function. (Parenthetically, one of the festschrift editors asked me to consider removing that suggestion.) In short, I proselytized. In addition to following one's curiosity, even if it involves some risk-taking, the need to proselytize one's scientific contributions is another bit of advice for PNIRS trainees. To paraphrase the classic Zen koan, if there is a connection between the brain and the immune system, and immunologists are unaware of it, is there still a connection? Of course there is, but I think that unless scientists present papers at meetings, visit other academic centers, and generally make themselves and their findings known, they run the risk of never fostering discussion, criticism, and new experimental ideas by others. I like to think that owing, at least in part, to my presentations and reputation in the 1970's and 1980's, at least some immunologists did take our research seriously.<sup>1</sup> Parenthetically, my job of spreading the gospel according to psychoneuroimmunology was made more difficult by the fact that some members of the lay public had interpretations of this field that made it appear flaky, if not downright onerous, to immunologists. I'll return to this situation later in this paper when I discuss some of today's abuses of psychoneuroimmunology.

In the 30 years since Bob Ader and I published our first conditioning study, we have all learned much about how the nervous and immune systems engage in their meaningful bidirectional dialogue. Phenomenology is now being replaced

by reductionism that includes analyses of signaling pathways, receptor upregulation/downregulation, etc. However, the basic tenet of psychoneuroimmunology—that interactions among the nervous, endocrine, and immune systems contribute to the maintenance as well as to the disruption of homeostasis—has broad phenomenological implications for a diversity of biological and biomedical areas of research. Specifically, the knowledge that behaviorally-associated immunological changes and immunologically-associated behavioral changes resulting from interactions of these two systems bears on our understanding issues pertinent to evolution, ethology, ecology, and aging (to name but a few fields) in addition to better understanding the immune and nervous systems in health and disease. Psychoneuroimmunology also relates to homeland security, science education, and the practice of conventional and complementary and alternative medicine. This paper will highlight just some of these global implications of psychoneuroimmunology.

## 2. The uses of psychoneuroimmunology

### 2.1. Psychoneuroimmunology and the immune system in health and disease

#### 2.1.1. Basic immunology

No longer can anyone doubt that the immune system is innervated by the sympathetic nervous system (SNS; Elenkov et al., 2000) and that cells of the immune system express receptors for immunomodulatory hormones and neuropeptides that they themselves can produce (Blalock, 2005). To me as an immunologist, the key question raised by these facts is whether SNS innervation and neuropeptide production by, and receptors on, leukocytes, can teach us more about how the immune system functions. During the early years of psychoneuroimmunology, skeptics argued that since immune responses can be generated entirely in vitro, innervation must be supportive, rather than essential, for immune responses to develop in vivo. The basic premise of this argument could be flawed, however, if in vitro immune responses are, in fact, not generated entirely in the absence of hormones and neuropeptides. Not only are these molecules found, albeit in trace amounts, in the serum supplements needed for optimal cellular functioning in vitro, but also antigen-stimulated lymphocytes in vitro may be producing neuropeptides (Blalock, 2005) that function in an autocrine fashion to facilitate generation of immune responses by cultured cells.

That SNS innervation plays an important role in immunity has repeatedly been tested by the classical experimental procedure of defecting innervation and observing whether attendant immune responses are changed. Chemical sympathectomy (using 6-hydroxydopamine) of animals as phylogenetically distant as fish, frogs, and mice, has clear-cut effects on a variety of in vivo and in vitro immune parameters. Studies from our laboratory with both *Xenopus* (Kinney and Cohen, 2005) and mice (Kruszewska et al., 1995) have revealed increased immune activity following

<sup>1</sup> I know that Virginia Sanders did as did our Dutch colleagues Rudi Ballieux and Cobi Heijnen (his doctoral student at that time).

sympathectomy. The majority of other studies have demonstrated, in an equally convincing fashion, that chemical denervation effects decreased immune responses (Madden et al., 1994; Sanders and Straub, 2002). Differences in the direction of responses associated with sympathectomy have been attributed to a variety of conditions associated with the different aspects of the immunization protocols. Regardless of the directional outcome of denervation (for discussion of this point see Madden, 2003; Moynihan et al., 2003), these alterations clearly support the idea that the SNS exerts some sort of tonic regulation of various immune system components.

In my opinion, the most important set of experiments revealing an essential role of innervation in the immune system has come from many years of focused research by Virginia Sanders and her colleagues (Sanders, 2005). Their earlier research revealed that in addition to their expression on B-cells, beta2 adrenergic receptors ( $\beta_2$ AR) are differentially expressed on murine T-cell subsets. Specifically, clones of Th1 cells, but not Th2 cells express the functional  $\beta_2$ AR that binds to catecholamines and their agonists and antagonists (Sanders et al., 1997). Either norepinephrine (NE) or the  $\beta_2$ AR agonist, terbutaline, stimulates the  $\beta_2$ AR receptor to modulate the level of Th1 cytokines produced (i.e., decreased IL-2 production by freshly isolated murine splenic native CD4+ T-cells) (Kohm and Sanders, 2001; Sanders et al., 1997, 2001). Clearly, anything that differentially regulates cytokine responses of the Th1 and Th2 variety can have a potentially important impact on the ensuing immune response. Kohm and Sanders (1999) have also convincingly demonstrated that NE stimulation of the  $\beta_2$ AR expressed on B-cells is necessary for the maintenance of an optimal primary and secondary Th2 cell-dependent antibody response in vivo.

More recently, this group has reported another level of regulation associated with catecholamines. Specifically, signaling through the  $\beta_2$ AR receptor alters expression of the critically important co-stimulatory molecule, CD86 or B7-2 (Kohm et al., 2002; Sanders, 2005). CD86 is present on antigen presenting cells including B cells. It regulates both T and B cell function and is essential for generating normal levels of antibody and for germinal center formation.  $\beta_2$ AR stimulation increases B cell receptor-induced CD86 expression on B-cells both in vivo and in vitro. Depletion of NE in vivo decreases levels of antigen-specific IgG1 production, cell proliferation, and germinal center formation. Stimulation of the B cell receptor, CD86, and the  $\beta_2$ -AR, intrinsically modulates the level of IgG1 and IgE produced on a per B cell basis (Kasprowicz et al., 2000). Additional cell signaling studies have revealed insights into the mechanisms by which CD86 expression is regulated (Podoji and Sanders, 2003; Podojil et al., 2004).

Recently, Sanders et al. (2003) have demonstrated that  $\beta_2$ AR knockout mice are immunologically normal. Some might interpret this to mean that these receptor–ligand interactions are trivial. Adopting this line of reasoning, however, could lead one to dismiss major histocompatibility

complex (MHC) class I molecules as trivial because MHC class I-deficient mice ( $\beta_2$ M-knockouts) develop normally, live, and display specific cytotoxic CD8-mediated reactivity despite reduced numbers of CD8 T-cells (Koller et al., 1990; Raulet, 1994). I submit that if a given biochemical or cellular pathway is important, not only will it be phylogenetically conserved, but failsafe or redundant mechanisms to achieve similar results will have evolved.

Some of the most provocative immunological findings in psychoneuroimmunology are the iconoclastic observations of Ed Blalock and his colleagues that cells of the immune system produce hormones and neuropeptides (Blalock, 2005; Smith, 2003). The remarkable diversity of these mediators has been well described as have the stimuli that elicit their production, and the nature of the leukocytes that produce them (Blalock, 2005). Although it is now clear that antigens, cytokines, and stressors regulate production of these leukocyte-derived peptides and hormones, the role(s) played by these leukocyte-derived molecules in immunity is not really understood. Given that these mediators are produced in small amounts, and that the leukocytes and innervating nerve fibers bear receptors for the mediators they produce, a most reasonable suggestion is that the peptide hormones and neurotransmitters produced by lymphocytes play an autocrine function. Machelska and Stein (2000) reported that lymphocyte-derived  $\beta$ -endorphin modulates pain sensations by acting on peripheral sensory nerves. It is also possible that these leukocyte-derived peptides may provide signals (feedback loop) to the CNS. For example leukocyte-derived alpha MSH has been shown to cross the blood brain barrier and affect signaling in the SNS. The role of immune system-derived molecules is an area of research that needs to be mined, but for reasons I don't fully understand, there are very few interested miners.

### 2.1.2. Psychoneuroimmunopharmacology and Psychoneuroimmunotoxicology

Defining the pathways and mediators associated with behavioral regulation of immunity, and understanding how manipulation of these pathways and mediators influences health and pathology are of obvious clinical importance. Thus, I am somewhat surprised that relatively few investigators are addressing questions inherent in an emerging field that descriptively could be titled psychoneuroimmunopharmacology. As an example of what might be accomplished in the future, consider the possibility that since  $\beta_2$ AR receptor ligation appears to be important in generating immune responses, the therapeutic use of  $\beta_2$ AR antagonists or agonists might well be worth studying in the context of autoimmunity. In this regard, it is noteworthy that oral salbutamol, a  $\beta_2$ AR agonist, reduces LPS-elicited cytokine levels in mucosal tissues. As such it might be useful in treating gut-associated inflammatory diseases, where cytokines play a major role (Eijkelkamp et al., 2004). As another example, consider the finding that alpha MSH, acting via the SNS, is anti-inflammatory (Delgado-Hernández et al., 1999), and that an opioid receptor antagonist has

been reported to be more effective than cyclosporin in prolonging rat renal allograft survival (Arakawa et al., 1992). A major problem in the clinical application of these and many other findings, of course, is the nonselective activity of these immune modulators. That is, one cannot use an opioid receptor antagonist in one setting and not expect to interfere with effects of triggering that receptor in other systems involving opioids.

Investigators now recognize that exposure to diverse chemicals that affect the nervous system may, in turn, affect the immune system and modulate protective responses to malignant cells and infectious agents or lead to development of neurodegenerative or autoimmune diseases (Lawrence and Kim, 2000). With few exceptions, however, no one yet appears to be devoting his or her research program to exploring the impact of a particular behavior on a given toxicant's influence on the neural-immune network (i.e., psychoneuroimmunotoxicology).

### 2.1.3. Heat shock proteins, stress, and immunity

Several years ago, my evolutionary immunobiology laboratory began studying the impact of members of the hsp70 and hsp90 families (specifically gp96) of heat shock proteins (hsps) on immunity in the frog *Xenopus*. Although we knew that hsps are typically induced by heat, cold, and glucose deprivation (ergo their designation as “stress proteins”), our interest in them at that time was not as psychoneuroimmunologists. Rather, we focused on their possible ancestral roles in immunity. Hsps limit protein aggregation, facilitate protein folding and act as molecular chaperones in all species studied, and molecular, biochemical, and serological characterization confirms extensive structural conservation of gp96 homologues (Hendrick and Hartl, 1993; Lindquist and Craig, 1988). Germaine to this paper are data from frogs and mammals revealing that the involvement of gp96 and hsp70 in innate and adaptive immunity also has been conserved during vertebrate evolution (Robert et al., 2001, 2003, 2004; Srivastava et al., 1998). A wide range of endogenous peptides, representing the antigenic repertoire of a particular cell (i.e., tumor, viral, and minor H-antigens) associate in vivo with hsps released from necrotic cells (Srivastava, 1993). These hsp:peptide complexes are immunogenic. For example, *Xenopus* gp96 effects in vivo MHC-restricted thymus-dependent immunity against minor H-antigens (Robert et al., 2002). Further, soluble complexes of peptides and either gp96 or hsp70 purified from autologous murine (Suto and Srivastava, 1995) or frog (Robert et al., 2003, 2004) tumors specifically immunize recipients against tumor challenges. Such immunity is abrogated by depletion of CD8<sup>+</sup> T-cells or macrophages during priming (Suto and Srivastava, 1995), and of CD8<sup>+</sup> or CD4<sup>+</sup> T-cells during the effector phase. Treatment of tumor-bearing mice with hsp purified from an autologous tumor retards progression of the primary tumor, reduces metastasis and prolongs life span (Suto and Srivastava, 1995). Gp96 per se (without peptide) can generate non-specific immune responses mediated by enhanced

cytokine production and non-specific killing (Robert et al., 2004).

Given the importance and the structural and functional phylogenetic conservation of hsp70 and gp96 in immunity, it seems reasonable to assume that increased expression of these hsps might significantly influence immune responsiveness. It is in this context that one should note the research of Campisi and Fleshner (2002) who reported that in rats: (a) hsp72 could be induced by physical stressors (intense exercise, inescapable electric tail shock) and (b) this up-regulation had consequences in terms of several parameters of innate immunity. More recently, Fleshner et al. (2004) noted a similar elevation of central and peripheral hsp72 following exposure of rats to a cat predator (psychosocial stressor); this response could be blocked or attenuated by adrenalectomy. To the best of my knowledge, no one has studied whether hsp-peptide complexes play any role in the mediation of those changes in innate or adaptive immunity that are causally associated with either physical and/or psychosocial stressors.

## 3. Psychoneuroimmunology and the nervous system in health and disease

Although “typical immunologists” still don't pay much attention to the fact that tissues of the immune system are innervated (see basic immunology text books), this basic finding has quite literally added another chapter to neuro-anatomical textbooks (Felten et al., 2003). In many ways, neurobiologists seem more amenable to psychoneuroimmunology than immunologists. For example, neural scientists, who have initiated collaborations with immunologists, have revealed that classic CD4 T-cells play a critical role in mediating facial motor neuron survival after experimental axotomy (Jones et al., 2005). Neurobiologists have also embraced the world of the immunologist by exploring the roles of centrally and peripherally produced proinflammatory cytokines (e.g., IL-1, IL-6, and TNF alpha). A few examples in the arena of cytokine research are worth referencing: (1) proinflammatory cytokines play a critical role in neuroinflammation and neuroregeneration (Lotan and Schwartz, 1994); (2) IL-1 acts on the vagus nerve to cause behavioral changes and illness symptoms (Danzer et al., 2002; Goehler et al., 2002); (3) IL-1 can act on the hypothalamus and pituitary to produce CRH and ACTH, respectively (Parsadaniantz et al., 1994); and (4) proinflammatory cytokines (e.g., IL-6) are correlatively, if not causally, associated with affective disorders that include major depression (Atanackovic et al., 2004; Irwin, 1999; Yirmiya et al., 2000), schizophrenia (Müller et al., 1999), and eating disorders (Nova et al., 2002).

### 3.1. Psychoneuroimmunology and evolution

#### 3.1.1. Brief overview

A neural-immune bi-directional dialogue occurs in all vertebrates studied, as exemplified by: the commonality of

neural innervation of lymphoid tissues (Flory, 1989; Kinney et al., 1994); the immune impact resulting from altering this innervation (Kinney and Cohen, 2001, 2005); and the role of neuroendocrine molecules in such fundamental processes as smolting<sup>2</sup> in fish (Maule et al., 1987) and metamorphosis in amphibians (Rollins-Smith and Cohen, 2003).

The reader who is interested in these descriptive aspects of neural-immune system interactions in invertebrate and vertebrate taxonomic classes should refer to a review by Kinney and Cohen (2001). In the course of preparing that review, we wondered about the earliest origins of these interactions with their attendant inflammatory and stress responses. Put another way, did the nervous system co-opt mediators used by the immune system, or did the immune system co-opt mediators that phylogenetically were used first by the nervous system, or did both systems co-evolve in concert? Although there are no definitive answers to any of these questions, this issue should first be addressed in invertebrate systems, since by the time adaptive immunity evolved in the jawed fish, neural-immune interactions were already operational. Although there are claims that invertebrates produce IL-1 and other proinflammatory cytokines, in the absence of cloning studies, the best that one can say about these molecules is that functionally and by virtue of immunoreactivity, they are IL-1-like (see Kinney and Cohen, 2001). This is an important arena for future evolutionarily significant research. To uncover the earliest origins of the integration of these systems, and to determine whether the neuroendocrine and immune systems evolved from a “common ancestor” (Ottaviani and Franceschi, 1997, 1998) prior to the appearance of a blood–brain barrier (Cserr and Bundgaard, 1984), studies are needed that exploit not only the invertebrates but the most primitive extant vertebrates, the Agnatha (hagfish and lampreys) that lack MHC, Ig, and TCR genes, and the elasmobranchs (sharks and rays), where these critical hallmarks of adaptive immunity emerge for the first time (Du Pasquier and Flajnik, 1999).

An important area of contemporary research deals with several non-cytokine molecules that are common to the innate defense systems of both invertebrates and vertebrates. Specifically, many investigators (e.g. Beutler and Poltorak, 2001; Hoffmann et al., 1999; Medzhitov and Janeway, 1998) have provided strong evidence of evolutionary parallels and conservation of ancient host defense pathways involving Toll receptors and NF- $\kappa$ B signaling in organisms that have been separated from mammals by many hundreds of millions of years. Given the molecular tools that allowed this new information to be generated, it would seem worthwhile to determine whether such receptors and signaling pathways might be subject to regulation by those mammalian-like neuroendocrine mediators that

also appear to have been phylogenetically conserved in invertebrates.

### 3.1.2. Mate selection

Of relevance to this discussion of psychoneuroimmunology and evolution (if one favors Darwinian evolution rather than intelligent design) is mate selection. I'll consider two pertinent examples. The first presents the hypothesis that acne is of psychoneuroimmunological relevance in the context of mate choice (Bloom, 2004) and the second deals with the role of the MHC in mate selection. At the risk of being repetitive, both acne and the MHC-associated regulation of mate choice have immunological, neurobiological, and behavioral components and as such, fit the definition of psychoneuroimmunology. Acne occurs primarily during adolescence as the result of hormonal changes that eventuate in effecting plugging of the sebaceous glands. Keratinocytes undergo hyperproliferation and abnormal differentiation. Sebum (lipid “gunk”) accumulates and serves as milieu for growth of the bacterium *Propionibacterium acnes*. There is a strong immunological component to acne since colonization by these bacteria triggers a classic inflammatory cascade that results in pustules and papules.<sup>3</sup>

Bloom (2004) proposes that there are also strong behavioral considerations associated with acne. She reminds us that we are attracted to those physical features of the opposite sex that reflect strength, aggressive dominance, health, nutritional status, age, fertility, and resistance to disease. Genes associated with “providing and protecting” are inherited. By contrast, physical features of the opposite sex such as infection and infestation foster aversion. Acne, she posits, provides such an aversive stimulus to prevent reproduction by adolescents who are ill-prepared to “hunt and gather.” How might this translate into evolution and psychoneuroimmunology? Bloom points out the fossil record suggesting that *Homo erectus* reached adulthood by 12 years of age without passing through an adolescent period. By contrast, modern man requires about 20 years to mature. This adolescence reflects a longer period of learning and a larger brain that requires longer development times. The prefrontal cortex (responsible for memory and language, good judgment, complex problem solving, planning and organization of goal-directed behaviors, control of impulses and emotions) is undeveloped at the start of adolescence; it fully develops by the early twenties. Bloom proposes that delaying the onset of sexual activity for a number of years post-puberty until mental capacities are heightened and subsistence and parenting education is complete, would have exerted a positive selective value. The

<sup>2</sup> A series of physiological changes that prepare juvenile freshwater salmon for entry into salt water, is characterized by increases in plasma thyroxine and cortisol levels (Maule et al., 1987).

<sup>3</sup> *Propionibacterium acnes* contributes to inflammatory pathology by: secreting extracellular products that attract neutrophils, lymphocytes, and macrophages, which accumulate within the follicular epithelium and the perifollicular infiltrate; stimulating neutrophils to release lysosomal enzymes that rupture the walls of the follicle, further stimulating an inflammatory response; activating complement; and releasing soluble factors that stimulate the release of IL-8 and TNF from macrophages.

bottom line is that acne, an inflammatory evoker of avoidance, coincides with adolescence. It is initiated at the onset of puberty by sex steroids and typically terminates in late adolescence/early adulthood, just about the time the prefrontal cortex becomes fully functional.

Less speculative than this acne story is the evolutionary importance of the MHC in mate selection. A large literature points out that mice prefer mates that are genetically dissimilar at the MHC (Penn and Potts, 1999). One postulated rationale for this is that heterozygosity at the MHC has an increased survival value when it comes to recognition of a wide array of pathogens. The ability of an animal to detect different MHC haplotypes through olfactory cues, and to select a mate based on that information, is not restricted to mammals. Salmonids appear to recognize odors associated with the MHC and select mates accordingly (Landry et al., 2001). Female sticklebacks use odors to try to achieve an optimum number of MHC class-IIb alleles for their offspring through mate choice (i.e., they “count” alleles) (Aeschlimann et al., 2003).

### 3.1.3. Stress pheromones and evolution

It is well known that odors from stressed conspecifics are released from the body surface and urine (Mackay-Sim and Lang, 1981) and function as “alarm signals” that can induce increased exploration in recipient rats (Mackay-Sim and Laing, 1980) as well as physiological changes in mice that include increased production of corticosterone (File et al., 1993; Fuchs et al., 1987; Marchlewska-Koj and Zacharczuk-Kakietek, 1990). Odors from stressed mice can also influence immunity in conspecifics (Cocke et al., 2003; Moynihan et al., 1994, 2000). Specifically, we have reported that exposure to odors (pheromones) from footshock-stressed mice suppresses cell-mediated immunity (IL-2, NK cell responses) and enhances humoral immunity (IL-4, anti-KLH antibody) in BALB/c odor-recipient animals. Glucocorticoid receptor antagonism with RU486 blocks the enhancement of IL-4, but not antibody titers (Moynihan et al., 1994). The opioid antagonist, naltrexone, however, abrogates the increase in IL-4 and anti-KLH antibodies as well as blocks the concomitant stress-odor increase in analgesia as determined by latency in the classic tail flick assay (Moynihan et al., 2000).

The question of whether there is a survival value to altering immunity in response to olfactory cues invites imaginative speculation. Consider, for example, a scenario in which a rabbit barely escapes to its burrow after having been wounded by a close encounter with an owl whose talons carry an infectious agent. If stress odors from that putatively infected rabbit effect an increased immune response capacity of other rabbits living in the same burrow, might not those animals be better equipped to deal with an infection by a fast-growing pathogen? Perhaps a more cogent related question is, whether “illness odors” (e.g., odors from purulent wounds) are also immunomodulatory? That animals can detect illness in conspecifics courtesy of pheromones is documented (Kavaliers et al., 2003; Zalaa et al.,

2004). Finally, in the context of evolution and the adaptive significance of pheromones as markers of immune or infected status, it’s worth noting that female mealworm beetles prefer pheromones from males with better immunocompetence as measured by faster rates of encapsulation of an antigen and by higher levels of phenoloxidase in hemolymph (Rantala et al., 2002). In other words, these pheromones appear to be conveying information about the males’ ability to resist parasites.

### 3.1.4. Immunological set points and evolution

If one accepts that the immune system evolved to protect individuals from pathogens, and that it coevolved with the nervous system in terms of bi-directional interactions, then it would seem counterintuitive that in a healthy organism, a brief exposure to an immunomodulatory stressors could “knock down” this protective system to the extent that the health of an animal is severely compromised. After all, the immune system evolved to function effectively over a wide numerical range of different cell populations that reside in multiple lymphoid compartments, and in healthy animals, regardless of whether they were acutely stressed (e.g., by a predator–prey event). If one accepts this, does it make sense, from a clinical perspective, to make a big deal over a stressor-associated small, albeit statistically significant, increase or decrease in a particular immune parameter being measured in a given compartment at a given time? From an evolutionary perspective, isn’t the critical question really whether a behavioral manipulation (e.g., stressor/intervention) affects immunity so as to affect health and survival? In this context of the clinical relevance of stress-induced immunomodulation, perhaps we should be focusing our research on the impact of chronic stressors and their immunomodulating activity in animals that are exposed to realistic concentrations of antigen that don’t generate an “optimal immune response” capable of masking subtle neuroendocrine modulations. Similarly, might it not be more revealing of the impact of stress on health to explore stressor-associated influences on immune responses of animals or humans that are experimentally or naturally immunocompromised (i.e., whose immune systems are operating at the nadir of various immune system set points). In this regard, it is important to note that stressor-associated impaired vaccination responses to influenza (Moynihan et al., 2004) or herpes zoster virus (Irwin et al., 2003) have been relatively easy to discern in elderly human subjects whose immune systems have been subjected to the natural immunosenescence of aging. Interestingly, the use of a behavioral intervention (Tai chi chih) to reduce the incidence and severity of shingles has proven to be effective in the elderly (Irwin et al., 2003). Moynihan and her colleagues have extended this idea by testing the hypothesis that it should be relatively easy to visualize effects of a stressor in an animal whose immune system has been diminished by the immunosuppressive drug CY. In this study (Cao et al., 2004), footshock stress plus CY resulted in reduced levels of IL-2, decreased levels of HSV-induced

IFN- $\gamma$ , and an earlier death relative to the appropriate controls that just received either footshock or CY. It also seems worthwhile to study the clinical outcome of stressors in those populations whose immunological set point deviates from normalcy owing to a viral infection (eg., HIV) or an autoimmune disease.

### 3.2. Psychoneuroimmunology and ecology

It may seem surprising to consider psychoneuroimmunology in the context of ecology. However, by using a little imagination, one can arrive at several under-explored scenarios in which environmental stressors of natural populations may influence an animal's very survival by affecting its immune system. Consider, for example, handling stress in the context of morbidity and mortality of seabirds that are cleaned after having been contaminated by an oil spill (Briggs et al., 1996). Or given that trapping and handling wild birds influences glucocorticoids (Romero and Wingfield, 1999; Romero et al., 1997), think about the fate of migrating birds, weakened by flight and lack of feeding, that are captured in mist nests, banded, and then released? Or ponder the immunological sequelae of strandings of cetaceans that appear to be the result of their exposure to high intensity sonar thanks to the US Navy (Romano et al., 1994).

#### 3.2.1. The amphibian decline problem

One ecological problem area that is being studied deliberately from a psychoneuroimmunological perspective is the worldwide decline of populations and species of frogs and salamanders (Collins et al., 2005). One cause of these declines and extinctions is clearly the destruction of habitat where amphibians breed and grow. A second cause is the stems from the introduction of superior predators or competitors that displace native species. At face value, these two explanations would not appear to involve psychoneuroimmunological considerations although they do involve what might be considered environmental stressors. However, we also know that two pathogens, a chytrid fungus (*Batrachochytrium dendrobatidis*) and iridoviruses (ranavirus, *Ambystoma tigrinum* virus) are causally involved (Carey et al., 1999) in the decline; so too are anthropogenic environmental changes or "ecological stressors" that include toxic chemicals, UV radiation, and/or global climate change. It seems reasonable to propose that these environmental variables are interacting, via neuroendocrine pathways, to suppress amphibian immunity and thereby increase fungal and/or viral pathogenicity (Rollins-Smith and Cohen, 2003). Studies of immunity to chytrids and ranaviruses are only in their infancy. Nevertheless, we do know that naturally produced antimicrobial skin peptides of frogs are capable of inhibiting growth of zoospores and mature fungal cells (Rollins-Smith et al., 2002). Secretion of these peptides from amphibian skin glands is regulated by the SNS (i.e., the catecholamines epinephrine and norepinephrine; Benson and Hadley, 1969; Dockray and Hopkins, 1975; Holmes and

Balls, 1978). Could environmental "stressors" (e.g., pesticides) be affecting peptide production/secretion via their effects on the sympathetics? Although this possibility has yet to be tested in a laboratory environment, we do know that chlorotriazine herbicides decrease the intracellular content and release of dopamine and NE from PC12 cells, a cell line with neuronal characteristics (Das et al., 2000, 2001, 2003). Also, a dithiocarbamate compound, similar to agents used as pesticides, inhibits NE synthesis by suppressing the activity of dopamine- $\beta$ -hydroxylase (Goldman et al., 1994). In other words, this possibility may not be far-fetched.

My amphibian research laboratory has been studying antiviral immunity in a model anuran, *Xenopus laevis*. We now know that in addition to antimicrobial peptides (Chinchar et al., 2001) and NK cells (Horton et al., 2003) as components of its anti-viral innate immune system, *Xenopus* uses CD8 T-cells, NK/T-cells, and antibody to deal with laboratory-induced infections with the iridoviruses, frog virus 3 (FV3; Gantress et al., 2003; Robert et al., 2005). We also know that X-irradiation increases mortality associated with FV3 infection (Robert et al., 2005). Metamorphosing frogs have a naturally down regulated immune system<sup>4</sup> and larval and metamorphosing frogs are much more susceptible infection with FV3 than are adults (Robert et al., 2005). Finally, we know that in amphibians, glucocorticoids are highly immunomodulatory, especially during metamorphosis (Rollins-Smith et al., 1997). In this regard, xenobiotic chemicals in the environment can induce increases in circulating corticosteroids (Gendron et al., 1997; Hopkins et al., 1999). Although we've not directly tested this possibility in *Xenopus*, we do know that elevated levels of corticosteroids have been detected in toads (*Bufo terrestris*) collected from areas polluted by coal ash (Hopkins et al., 1999), and in mudpuppies (*Necturus maculosus*) that have been exposed to organochlorine (Gendron et al., 1997) in a setting in which maximal concentrations approximate those associated with the natural glucocorticoid-associated immunosuppression in *Xenopus* that occurs during metamorphosis (Barker et al., 1997; Rollins-Smith and Blair, 1993).

### 3.3. Psychoneuroimmunology and ethology

Given the "P" in psychoneuroimmunology, it is self-evident that the behavior of an animal may influence its immune system. Most of us, however, erroneously think of the immune impact of behavior only in the context of laboratory environments and in humans, rather than whether the normal behavior of feral animals can be immunomodulatory. There is a significant literature on glucocorticoid levels in the context of social dominance and submission of cooperative breeding carnivores like dwarf mongooses, wild dogs, and wolves (Sands and Creel, 2004). However there does not appear to be

<sup>4</sup> It is thought that this downregulation evolved to protect animals from immune responses to adult-specific antigens that are emerging during the metamorphic transition from immunocompetent larva to immunocompetent adult.

any information relating chronically elevated steroids to altered immune function and disease in these species. On the other hand, Sapolsky and colleagues (Alberts et al., 1992; Sapolsky, 2005) have considered endocrinological and immunological parameters in the context of the social organization of baboons; their immunological data, of course, are limited owing to difficulties inherent in field studies.

Another behavioral area of significant interest to “psychoneuroimmunologists” pertains to energy trade offs among diverse physiological processes. For example, behaviors such as nest building (Lochmiller and Deerenberg, 2000; Martin et al., 2003) or feeding nestlings (Moreno et al., 2001) are energy demanding and as such, “take energy” from those processes needed to mount an immune response (i.e., they compromise the immune response). Conversely, the activation of an immune response is beneficial for organisms but may also have energy costs that affect fitness.

### 3.4. Psychoneuroimmunology and aging

I’ve already mentioned aging in the context of lower immunological set points and stress. Now let’s consider a recent paper in the PNAS by a team at the University of California at San Francisco (Espel et al., 2004) that addresses the potential impact of a stressor on the aging process itself. These investigators found that perceived chronic caregiver stress in healthy women was associated with shortened telomeres, reduced telomerase activity, and increased oxidative stress in peripheral blood leukocytes. All these changes are normally associated with the aging process. It remains to be determined whether these cellular markers of aging affected by stress are restricted to blood cells. It also remains to be discovered whether these observations can be generalized to a variety of chronic stressors and whether psychological interventions designed to alleviate stress (e.g., mindfulness based stress reduction; Kabat-Zin, 1982; Carlson et al., 2003) can reverse or stop the accelerated aging process associated with caregiver stress.

### 3.5. Psychoneuroimmunology and homeland security

These times provide ample examples of situations in which large numbers of individuals are exposed to chronic as well as acute stressors associated with natural (e.g., the tsunami of 2004; hurricanes Katrina and Rita in 2005) as well as man-made disasters. With respect to the latter, there is a literature on the impact of 9/11 on the development of posttraumatic stress disorder (PTSD)-like symptoms in New Yorkers (Galea et al., 2002; Hoge et al., 2002) and on the impact of PTSD on immune function (Altemus et al., 2003; Kawamura et al., 2001). Whether these psychological consequences of 9/11 have, or will, translate into changes in the frequency and severity of infectious diseases or other immunologically-associated pathologies remains to be seen. The same question, of course, must be raised for the civilian population in war-torn Iraq.

Psychoneuroimmunology should also be of interest to the military since soldiers are exposed to a plethora of stressors that influence immunity in civilian populations. These include: exercise associated with military training; separation from one’s family; battlefield conditions (e.g., driving a truck along a highway strewn with hidden improvised explosive devices); sleep deprivation; and bereavement. We also know that a high frequency of returning veterans suffer from PTSD and immune system changes (Boscarino and Chang, 1999), but the toll of PTSD and the aforementioned stressors on the development of immunologically related disease processes remains to be evaluated.

Our military receive a battery of vaccines during training and before deployment. That their perceived stress during the period of vaccination might impair their immune responses to vaccines is another point that should be of some concern (Burns et al., 2003).

Dolphins are part of the US Navy’s military “arsenal.” For example, they are trained to detect and plant mines on ships. Given that these marine mammals are exposed to significant stressors inherent in their capture and transport, and associated with their social instability and unstable dominance hierarchies in their pens, it should come as no surprise that these animals might be at an increased risk of infectious diseases (Waples and Gales, 2002).

### 3.6. Psychoneuroimmunology and complementary and alternative medicine (CAM)

Psychoneuroimmunology should be providing the scientific underpinnings for validation of nonconventional therapeutic modalities that pertain to immune system outcomes. However, it is rare, but not impossible (see Irwin et al., 2003), to find papers in peer-reviewed scientific journals that address *clinically relevant* immunological changes resulting from Reiki massage, guided imagery, therapeutic touch, or other so-called alternative stress-reduction interventions. Is this literature so limited because no one is studying these CAM procedures in the context of psychoneuroimmunology, or have the appropriate studies been conducted without the anticipated immunological changes? The possibility that only limited financial resources are available for such studies seems questionable since the NIH’s National Center for Complementary and Alternative Medicine (NCCAM) was developed to fund solid scientific exploration of such issues. Yet, a search of the NIH CRISP database reveals that most of the studies supported by NCCAM in 2005 focus on the impact of herbal medicines, acupuncture, placebos, touch, etc. on nonimmunological outcomes. Indeed, by my count, only a dozen or so of the NCCAM-funded studies in 2005 can be construed as having a psychoneuroimmunological thrust.

### 3.7. Psychoneuroimmunology and science education: Are we doing our job?

Ten years ago, the cultural anthropologist, Emily Martin, published a book entitled “*Flexible Bodies: Tracking*

*Immunity in American Culture From the Days of Polio to the Age of AIDS* (Martin, 1994). Among other things, Professor Martin describes her studies revealing just what the American public knows about the immune system. Although I think that one of the responsibilities of immunologists is to educate the public about immunology, this section of Martin's book points out that we may not really be doing our job. When I mention to nonscientists that I'm an immunologist, more often than not, I receive a blank stare. However, when I say something to the effect that I'm studying how the mind and behavior affects those physiological systems that protect us against disease-causing germs, the glazed-over expression is replaced by an apparent understanding. Something about psychoneuroimmunology resonates with the public, resonates so much so that this field has truly become popularized. After all, everyone "knows" what stress is and believes that all stress is bad. People also believe they should be actively engaged in a life style (nutrition, exercise, positive thinking, etc.) that is "known" to be healthy and, at least according to advertisements, will "boost" their immune systems.<sup>5</sup> People want alternative approaches to health care (Eisenberg et al., 1998), and since psychoneuroimmunology carries the imprimatur of hard science, it has become the epitome of mind–body medicine. I also think that the acronym PNI has had something to do with the popularization of the field. It's catchy and easy to remember; googling PNI produces more than 400,000 hits. However, it may come as a surprise to the reader of this journal that PNI is not only an acronym for psychoneuroimmunology.<sup>6</sup> In part because of these alternative meanings, I have refrained from using the PNI acronym anywhere in this paper. In my writings, I also don't refer to physical chemistry as P. Chem. or to evolutionary immunobiology as EB. To me, the acronym PNI has invited the nonscientist to develop an uneducated, inaccurate familiarity with the subject that, in turn, has led to a distortion of what our field is really about. In fact, I submit that in 2005, education of the public in immunology as it relates to psychoneuroimmunology has been skewed more by hype and hope rather than by reality. When one "googles" psychoneuroimmunology, one ends up with more than 80,000 hits. Some of the on-line material, of course, is real science, but much of it is not. In short, the popularization of psychoneuroimmunology has led to commercialization, misinterpretation, and oversimplification of the field.

<sup>5</sup> When I see advertisements to boost my immune system, I cannot help but wonder what good would it do to have an immune system operating at 150% capacity when 100% activity has been sufficient for millions of years. On the other hand, should any of these immune boosting nostrums be effective, couldn't such an immune "boost" result in autoimmunity and/or increased allergic responses?

<sup>6</sup> Consider for example: Precision Navigation; Pacific Neuropsychiatric Institute; Postnatal Illness; Pharmaceutical News Index; Pacific Northwest Index; Philadelphia Newspapers; Performance Network; Portanails; Public Nonprofit Institutions; Plastics News International; Partnership for Neighborhood Improvement; and last but not least, Parti pour la Normandie Indépendante.

Some of these abuses are considered in the following section.

### 3.8. *The abuses of psychoneuroimmunology*

When I delivered the 2005 Cousins platform address in Denver, I was not particularly concerned about naming individuals whose websites reveal gross misinterpretation of the field and who, in my opinion, are misguiding the public. Although I am more reluctant to put those names in print in a scholarly journal, I still think it is important to recognize just how much flawed information is being promulgated on the Internet. Consider, for example, a retired neurobehavioral Ph.D. with self-proclaimed training in the neurological aspects of olfaction, psychoneuroimmunology and aromatherapy, who now practices as a wellness consultant, healer, Reiki master, and personal development coach. She is founder and owner of Dreaming Earth Botanicals, producers of SomaTherapy Essential Oils, and she provides consultation to individuals, physicians, and holistic practitioners. Or consider the following quote on page 178 from a book by Patricia Davis (Davis, 1992) entitled "Aromatherapy An A to Z." "Essential Oils can support and strengthen the immune response in two ways, by directly opposing the threatening microorganism and/or by stimulation and increasing the activity of the cells involved. Lavender, Bergamot, Eucalyptus, and Rosemary all act against a wide variety of bacteria and viruses while at the same time increasing the immune response. Rosemary and Geranium support the adrenal glands in their action and are also stimulants of the lymphatic system. Black Pepper and Lavender have a beneficial action on the spleen." Although future research may demonstrate significant immunomodulatory abilities of the aforementioned plant extracts, now, in the absence of data supporting such claims, snake oil cures would seem to be for sale.

The popularization of psychoneuroimmunology has evolved a "new age" jargon that obfuscates the real meaning of psychoneuroimmunology. Consider for example, a book by Jane Alexander (1998) entitled "The Detox Plan for Mind, Body, and Spirit." Although I admit I've only read about this self-help book on-line, I was struck by its having a section titled "Psychoneuroimmunology (Pni)," which is defined as the mind's ability to effect change in the body. Although I don't necessarily argue with this broad vague definition, I do object the author's next statement claiming that "the major technique in psychoneuroimmunology is visualisation," where patients are "taught to focus their mind to visualize healing energy flowing into ailing organs, to dissolve tumours, repair tissues and so forth." I am also bothered by the fact that the brief mention of psychoneuroimmunology is flanked by sections titled: "Energy Medicine;" "Forms of Vital Energy;" "Balance Your Chakras for Health and Harmony;" "Healing the Chakras;" "Auras: What the Various Colors Mean;" "What does Prayer Mean to You;" "Mantras: A Different Form of Prayer;" "Finding the Kind of Prayer that Works for

You;” and “Toning the Names of God.” To me, the company kept by that section on psychoneuroimmunology, a scientific discipline, makes me feel used; perhaps actually reading the chapters will make me feel even more exploited.

I also discovered the website of a clinical neuropsychiatrist who established the Institute of Biocognitive Psychology in 1998. In a forum section, he boldly and definitively states that the immune system responds to so-called “righteous anger” by increasing NK cells but it responds to a form of anger resulting from “pseudo indignation” by depleting NK cells (<http://www.biocognitive.com/Forum/0021.htm>). Live and learn.

I’ll conclude this somewhat acrimonious listing of abuses by pointing out that Alphasonics International produces a subliminal tape on psychoneuroimmunology. The advertising blurb for this item as listed on eBay claims that these tapes are “designed to help your mind strengthen your natural immune system, ward off disease, and attain vibrant health. They suggest such ideas as my body is healthy, my immune system is strong, all my cells function perfectly, my organs are renewed. I am vital and whole.” Are further examples really needed to make the point that what the public learns about our field of psychoneuroimmunology from the web is not what’s available in the third edition of “Psychoneuroimmunology” (Ader et al., 2001)? Why do I care about such abuses? In part, it’s because I think the public would do just fine if every site they checked out had information that was scientifically validated. I also care because I think my colleagues in other areas of immunological research (especially those who review our grants) may be getting a tainted view of the field.

To end this section on an upbeat note, I actually believe that some alternative treatments that are currently based on the personal belief systems of their practitioners (i.e., aromatherapy, therapeutic massage) may indeed become validated as scientists apply rigorous criteria to evaluating their efficacy and modus operandi in solid clinical trials.

#### 4. Concluding remarks

In the first chapter of his autobiographical notebook, “Human Options,” Norman Cousins wrote: “The most important thing I have learned is that one of the prime elements of human uniqueness is the ability to create and exercise new options. The ultimate test of education is whether it makes people comfortable in the presence of options; which is to say, whether it enables them to pursue their possibilities with confidence. Similarly, a society can be judged according to the number and range of options of consequence it makes open to its people.” If one applies Cousins’ ideas to the establishment of the field of psychoneuroimmunology in the 1970s and 1980s, George Solomon, Bob Ader and I, David Felten and Suzanne Stevens, Ed Blalock, Hugo Besedovsky and Adriana del Rey, John Hadden, Tom Roszman, and several other investigators were exercising their options, their “natural right,” to pursue observations and novel ideas. Personally, this is why I became a

scientist. Nowadays, however, I worry that by restricting federal research dollars and thereby restricting opportunities for novel ideas to develop and flourish, society may be reducing the number of “options of consequence” it makes open to people.

Owing to space constraints I’ve limited my remarks about the global ramifications of psychoneuroimmunology to immunology, neurobiology, pharmacology, toxicology, ecology, evolution, ethology, gerontology, homeland security, science education, and CAM. I’ve not considered additional options for psychoneuroimmunology revealed by contemporary research in: sleep (Krueger et al., 2001); exercise physiology (Suzuki et al., 2003); pain (Page et al., 2001; Watkins and Maier, 2002); wound healing (Glaser et al., 1999); regeneration (Lotan and Schwartz, 1994); coronary artery disease (Kopp and Cohen, 2001); obesity and leptin physiology (Loffreda et al., 1998; Lord et al., 1998); gastric ulcers (Weiner and Shapiro, 2001); affective disorders (Atanackovic et al., 2004; Irwin, 1999; Müller et al., 1999; Yirmiya et al., 2000); pregnancy (Coussons-Read et al., 2005); and several other research areas that are covered in chapters in the third edition of *Psychoneuroimmunology* (Ader et al., 2001) and elsewhere. In short, it should now be obvious to all those in the biomedical sciences that bi-directional interactions among behavior, the nervous system, and the immune system, cannot help but have global consequences.

Necessitated, at least in part, by the realities of today’s funding priorities, we are strongly “advised” to propose mechanistic hypothesis-driven studies, rather than so-called phenomenological research, in our applications to garner NIH funding. Nevertheless, I believe there is still the need for a phenomenological approach to research. When I used to lecture about our conditioning studies, a common question from the audience was “how does it work?” This is a naïve (albeit valid) question since if I were to answer it with any approximation of accuracy, I would have to know just how the CNS works and how the immune system works before trying to figure out how the dialogue between the two systems is triggered by the presentation of a conditioned stimulus. Although some of my colleagues have posited various central pathways that are operational in their particular conditioning paradigm, I would argue that they really don’t know *all* the pathways that are no doubt involved in all the paradigms associated with conditioned immune modulation. What is the likelihood that the central mechanisms responsible for conditioned immunosuppression with CY and saccharin (Ader and Cohen, 1975) are the same as those that are operational in conditioning increased antibody responses by pairing an antigen with a gustatory stimulus (Madden et al., 2001)? Our collective failure in not understanding all these mechanisms doesn’t mean that immunomodulatory changes can’t be achieved by conditioning. If in 1974, Bob Ader and I had avoided initiating our conditioning studies because if they “worked,” we would not be able to decipher the underlying mechanisms in our life times, I wonder whether this paper could have been written, and whether *Brain, Behavior,*

and Immunity and the Norman Cousins Memorial Award would have existed.

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