Psychoneuroimmunology

The Interface Between Behavior, Brain, and Immunity

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Psychoneuroimmunology is the study of interactions between behavior, the brain, and the immune system. This article is designed to provide an overview of this new field for the general psychologist. The existence of bidirectional communication pathways between the brain and the immune system and the implications of this network for behavior are emphasized. Implications are that behavioral–psychological processes ought to be capable of altering immune function and that events that occur as part of immune responses should modulate behavior. Evidence for influences in both of these directions is reviewed. The discussion of psychological modulation of immunity focuses on classical conditioning and stress, whereas that of immune modification of behavior highlights behavioral effects produced by substances released by the immune system. Finally, the adaptive role that such changes might play is considered.

The purpose of this article is to provide psychologists with an overview of the new field of psychoneuroimmunology (PNI), which has developed over the past 10 to 15 years. A detailed review is not possible here; various aspects of PNI have recently been given extensive review (Ader & Cohen 1993; Ader, Felten, & Cohen 1991; Cohen & Williamson, 1991; Kemeny, Solomon, Morley, & Bennett, 1993; Plotnikoff, Murgo, Faith, & Wybran, 1991). Neither is the purpose to review our own work in this area. Instead, our goals are to provide (a) a sketch of the basic core facts that led to the coalescence of a new discipline, (b) some indication of the possible functional significance of the basic aspects of organization that have been discovered, (c) a feel for some of the exciting possibilities provided by PNI, and (d) some cautions to note. We will concentrate on the "whys" rather than provide a list of studies. For example, in our discussion of stress and immunity we will not provide extensive documentation that stress can alter immune function—that is well-known and has often been reviewed. The "hows" (what type of stressor, which hormone is the critical mediator, etc.) have also been reviewed elsewhere. Instead, we will attempt to rationalize why it is that stress alters immunity and why this might be adaptive and functional, or might have been adaptive in evolution, rather than simply being a curiosity. These are the questions that psychologists typically ask when they are presented with work in this area. Discussions such as these often will be, of necessity, quite speculative. However, it is our belief that the psychologist will be as captivated by this field as we are only if some of these evolutionary–functional possibilities are elaborated, so that the connections between behavior and immunity come to make intuitive sense.

PNI is the study of interactions between behavior, the nervous system, and the immune system. It grew from the realization that the immune system does not operate autonomously, as had often been supposed. The typical view, held as recently as 10 years ago, was that the immune system was a closed system. It was thought to be driven by challenges from foreign substances (antigens) and regulated by soluble products produced and released by immune cells (lymphokines or cytokines, more generally). These products serve both to communicate between immune cells both locally and at distant sites and to control the progress of the immune response. Although antigens do initiate immune responses and cytokines do regulate immune processes, a wide array of recent research demonstrates that there are bidirectional communication pathways between the immune system and central nervous system (CNS), with each providing important regulatory control over the other.

As will be noted, immune function can require global alterations involving the entire organism (e.g., a shift in energy balance) as well as the more usually considered local processes (e.g., selective rapid multiplication of T cells in a lymph node in response to a detected antigen). Only the CNS can orchestrate such widespread outcomes in a coordinated fashion. Thus the CNS must

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be able to exert control over some aspects of the immune response. Conversely, in order to accomplish this function, the CNS must receive information about events in the body (e.g., an infectious agent has penetrated the skin) and the status of immune processes. Indeed, the immune system serves as a diffuse sensory organ to provide the brain with a variety of input. Thus the immune system controls neural function, and the CNS controls the immune system. Of course, the existence of neural–immune interactions permits behavioral–psychological events to enter the matrix; if neural processes regulate immune processes, then there is a pathway by which psychological factors could impact immunity. Conversely, if immune processes alter neural function, then they can also potentially impact on behavior, emotion, and thought. PNI, then, is the study of these complex interactions between neural, immune, and behavioral processes.

The multidisciplinary nature of PNI makes this review somewhat complex. We ask the reader to bear with us, for we believe that this field is of great potential significance for psychologists. A brief preface might help orient readers and keep them aware of why specific topics are included and presented in the order that they are. We begin with a brief description of the immune system, as many readers may not be familiar with its organization, and without some understanding, it is not possible to see how interactions between behavioral and immunological processes might be adaptive. (Readers familiar with basic immunology can easily skip this section.) We next describe why it is that the immune system is now thought to be under neural regulation. After establishing the basis for thinking that there is a communication pathway between the CNS and the immune system, we briefly review what is known about psychological modulation of immune function. We then consider the other direction in the bidirectional pathway between the immune system and the CNS and review connections from the immune system to the CNS and immune modulation of behavior. The final section focuses on the functional significance or the reasons why—why would it be reasonable for stress, for example, to impact on immunity and why the observed pattern of behavioral changes that occur during immune challenge are both logical and adaptive. This section delves into the evolution of immunity, the costs of immunity (any biological process has costs as well as benefits), and issues of energy balance to attempt to come up with a rational set of reasons. The point of view that we develop is speculative, frankly, but it makes sense to us. We end with some conclusions and the hope that we have convinced the readers that this field is on to something.

The Immune System

The purpose of this section is to provide the necessary basics to understanding interactions between behavior and immune function. The major thought is that the specific immune response to an invading pathogen (virus, bacteria, etc.) is a process that extends over many days and requires complex coordination between many different types of cells that have to interact with each other in very circumscribed ways. It is a dynamic process over time, not a discrete or punctate response.

The immune system is so-called from the Latin term *immunis*, meaning "exempt," and is the body's defense against invading pathogenic microorganisms and tumors, as well as being an important component of tissue repair processes after injury. It is divided into *innate* (or nonspecific) and *specific* acquired immunity. Innate immunity refers to one's resistance to pathogens, which is present from birth and which operates in a nonspecific way without regard to the exact nature of the pathogen (e.g., whether it is a pneumococcus bacterium, a polio virus, or some other). There are a wide variety of innate immune defenses. Some are anatomical (e.g., the skin prevents the entry of many pathogens and its acidity limits bacterial growth), some are physiological (e.g., mucus contains substances that can destroy bacterial cell walls), and some are phagocytic (e.g., macrophages can engulf and destroy microorganisms that they contact). Perhaps the most important innate defenses are provided by the inflammatory and acute phase responses, which will be described later.

Specific immunity is acquired, rather than innate. It involves two separate but related processes—recognition of foreign, "nonself" substances called *antigens* (derived from "antibody generator") and destruction (removal of antigen). T and B lymphocytes are critical to these processes. T cells arise from progenitor cells in the bone marrow and migrate to the thymus where they mature. After maturation, the T cells circulate through the blood and lymph and often reside in secondary immune organs, such as the spleen, and lymph nodes. Each T cell has an exquisitely selective receptor on its surface that can recognize and bind only a single antigen. A given T cell has many receptor sites, but they are all specific for a same single antigen.

T cells cannot recognize antigens by themselves. Instead, the antigen must be presented to T cells in a processed form. Antigen processing and presentation is most often accomplished by immune cells called *macrophages*. Macrophages engulf and digest the antigens. They then excrete chunks of the digested antigen, and these antigen fragments bind onto the exterior surface of the macrophages. It is this processed macrophage-bound form of antigen with which the T cells interact. Thus the macrophages bearing the antigen must contact those few T cells that happen to have the receptor for that antigen. Because there are on the order of 10^{15} different T-cell receptors in humans and each T cell has only one type of receptor, it follows that there cannot be very many T cells with a receptor for any particular antigen. Obviously, to be able to defend oneself against foreign invasion, one needs to quickly create many T cells with a receptor for the antigen that has now invaded the body, so that the antigen can be attacked effectively.

T cells circulate in an inactive form, so the first task is to activate the T cells with the appropriate receptor. To do this, the macrophages release a cytokine called *interleukin-1* (interleukin refers to chemicals that are used to

communicate between leukocytes or white blood cells), which activate T cells. There are several different types of T cells. One, the T helper, becomes activated and secretes other cytokines that control the progress of the immune response. For example, the activated T helper cell releases interleukin-2, which promotes multiplication and maturation of T cells that are specialized to fight the antigen that began the process. The cytokines released by the T helper cells also help cytotoxic T cells to multiply, if they are specialized for killing the invading pathogen (i.e., have the appropriate receptor), whether it is an antigen-bearing microbe or antigen-infected cell. Thus the effector of this type of immune defense, called *cellular immunity*, because the killing is being done by a cell, is the activated cytotoxic T cell with a receptor that can detect and bind the antigen. Note that this whole process takes several days, inasmuch as it extends from detecting an invader to creating an army of cells to fight it. Finally, memory T cells develop that have a very long life span and can rapidly recognize the antigen if it is encountered again.

B cells mature in the bone marrow. They also have specific receptors on their surface, but they have a different structure than the T-cell receptor and are called *antibody molecules*. When a B cell encounters the antigen that can bind its receptor (membrane-bound antibody), it begins to divide, and its progeny differentiate into memory B cells and plasma cells. This process is aided by a large number of different cytokines secreted by activated T helper cells. This is a complex multiday process that is orchestrated by interleukins secreted by T helper cells. The T helper cells release different interleukins in a very specific sequence across days, which control the maturation of memory and plasma B cells. The plasma cells develop a new form of its surface receptor that does not remain membrane bound but rather is secreted as a soluble receptor into the circulation. These antigen-specific receptors released from plasma cells are called *antibodies*. The antibody will bind the antigen wherever it comes into contact with it and functions as the effector of this form of immunity, called *humoral immunity*. The process of binding the antigen by antibody is sometimes sufficient to eliminate it. In addition, the bound antigen–antibody complex can activate a blood system called *complement*, which can destroy the antigen. The process of generating antibody takes roughly five or more days. If the antigen is encountered again in the future, the antigen-specific memory cells can produce a much more rapid and potent reaction.

In sum, innate immune mechanisms operate as a first line of defense against invading pathogens. However, the nonspecific nature of the processes allows some pathogens to escape. Specific immunity enables the development of defense responses to a staggering number of potential antigens. Unfortunately, the specificity of the mechanisms involved requires that the response will be slow and delayed, because receptor specificity means that there cannot be many lymphocytes with receptors for any particular antigen. This means that lymphocytes specific to the antigen have to multiply greatly before a defensive response can occur, and the biology of cell proliferation is such that it requires several days. Fortunately, the memory processes built into the specific immune response allow a further encounter with the antigen to be dealt with much more rapidly. This is where the specific response is most effective.

Connections From the Central Nervous System to the Immune System

The purpose of the following discussion is to provide the basics of how it is that we know that the brain regulates the immune system. Two conditions would have to be demonstrated. First, the brain would have to make physical contact with the immune system in some way. Second, alterations in the activity or integrity of these connections would have to affect the course of immune responses to antigens.

The first question one might ask concerns how the brain is able to connect with and control other peripheral processes. The brain has two ways to control peripheral organs and processes. One is through the peripheral nervous system. The autonomic nervous system, composed of sympathetic and parasympathetic branches, innervates visceral organs such as the stomach and the heart. Research conducted during the past dozen years (e.g., D. L. Felten, Ackerman, Wiegand, & Felten, 1987) demonstrated that the sympathetic nervous system innervates immune organs such as the thymus, bone marrow, spleen, and, even, lymph nodes. Sympathetic nerve terminals release the catecholamine, norepinephrine, and immune organs and cells contain catecholamine receptors. Furthermore, the terminals of sympathetic nerves in these immune organs make contacts with lymphocytes themselves, and these contacts have the ultrastructural features of synaptic contacts (S. Y. Felten & Felten, 1991). Thus the brain is physically connected to the immune system.

The other way in which the brain can communicate to peripheral organs is by releasing factors that cause endocrine glands to secrete hormones into the circulation, thereby enabling the hormones to reach the various organs and bind to hormone receptors on the organs. An example that will be of particular relevance later in this article concerns hormones produced by stress. Many of the bodily effects of stress are produced by steroid hormones called *glucocorticoids*, which are released from the outer portion (cortex) of the adrenal glands. Indeed, the presence of stress is often defined by the existence of high levels of these hormones in the blood. The sequence of events is that both physical and purely psychological stressors lead cells in the paraventricular nucleus of the hypothalamus to synthesize and release a substance called *corticotropin* releasing hormone into the portal blood system at the base of the brain. This hormone then reaches the anterior lobe of the pituitary gland where it leads to the synthesis and release of adrenocorticotrophic hormone into the blood. This pituitary hormone ultimately arrives at the adrenal gland where it causes release of the glucocorticoids. The concept is that the brain released

something that led to hormones being released into the general circulation. T and B cells have receptors for many of these hormones, including the stress hormones just noted (Plaut, 1987). Activation of the sympathetic nervous system by stressors also leads to the release of catecholamines (i.e., norepinephrine and epinephrine) from the inner portion (medulla) of the adrenal gland into the blood; lymphocytes have catecholamine receptors as well. It is important to appreciate that immune cell function is altered by the action of these hormones and transmitters at receptors on the lymphocytes.

In sum, the anatomical arrangements are such that the brain could control immune cells and organs in the same ways it controls other peripheral structures. However, the fact that the brain can does not mean that it does. Is there evidence that the brain does participate in controlling normal immune responses? If the brain participates in the regulation of the immune system, then brain lesions and stimulation at some brain site(s) ought to modulate some aspect(s) of immune responses. The hypothalamus plays a key role in integrating neural control of visceral processes in general, and so it is not surprising that lesions of the hypothalamus alter the course of a variety of immune processes. This is true for in vivo measures of immune function such as antibody production and rejection of tissue transplants (Macris, Schiavi, Camerino, & Stein, 1970) and in vitro measures such as stimulated lymphocyte proliferation (Roszman, Cross, Brooks, & Markesbery, 1985). Moreover, lesions in other regions can also alter immune function (Nance, Rayson, & Carr, 1987). Conversely, electrical stimulation of hypothalamic regions has been reported to augment several immune parameters (Korneva, 1967). With regard to the autonomic nervous system, chemical destruction with 6-hydroxydopamine can impair some aspects of immune function (Livnat, Felten, Carlson, Bellinger, & Felten, 1985). The point is that destruction or stimulation of neural pathways that are connected to the immune system do, in fact, alter the function of the immune system, and so the connection between the CNS is of real significance, not merely an anatomic curiosity. Similarly, blocking the hormone receptors on lymphocytes alters the course of immunity (Blalock, Smith, & Meyer 1985).

Psychological Modulation of Immunity

The interactions between the CNS and immunity summarized above suggest that psychological events should be capable of altering immunity, because such events both alter and are expressed in neural activity and neural events make contact with the immune system. Research concerning psychological modulation of immunity has centered on two topics—classical conditioning of immunity and the impact of stress.

Classical Conditioning

Processes under the control of the CNS are generally modifiable by associative processes. Modern interest in the conditioning of immune responses stems from a study by Ader and Cohen (1975) in which a taste paired with an immunosuppressive drug in a Pavlovian manner acquired the ability to suppress antibody responses to an antigen. A large amount of subsequent research (see Ader & Cohen, 1993, for a review) has confirmed the generality of this finding across conditioned stimuli, immunomodulatory unconditioned stimuli, and immune measures. The initial studies used animal subjects, but conditioned modulation of immunity has also been demonstrated in humans (Smith & McDaniels, 1983). Furthermore, both immune suppression and enhancement of the immune response can be conditioned as well (Solvason, Ghanta, & Hiramoto, 1988).

Two questions are at the heart of current research concerning conditioned immunomodulation. One concerns the mechanisms involved: Are the immune changes "directly" conditioned or is something else conditioned (e.g., fear, anxiety, aversion, glucocorticoid release) that is then responsible for the immune alterations? The second involves the potential practical implications of conditioned immunomodulation. Could conditioned immune responses occur in real-life settings and influence disease processes, and could conditioning procedures be used in clinical settings?

Indeed, there is promise of clinical application. In a classic study, Ader and Cohen (1982) explored the development of systemic lupus-erythematosus-like autoimmune disease in genetically prone mice. The onset of lupus symptoms can be retarded and survival prolonged by immunosuppressive drugs such as cyclophosphamide. A neutral stimulus (saccharine flavored water) was paired with cyclophosphamide in a Pavlovian manner. That is, rats were allowed to drink the solution and then were immediately injected with cyclophosphamide. Weekly treatments with cyclophosphamide are required to delay the onset of lupus symptoms; administration of cyclophosphamide every other week has no measurable effect. However, Ader and Cohen (1982) found that the saccharine solution could be substituted for cyclophosphamide every other week and delay the onset of the autoimmune disorder, but only if it had been paired with cyclophosphamide (also see Klosterhalfen & Klosterhalfen, 1983). Moreover, reexposure to the saccharin cue after the cyclophosphamide treatment was discontinued prolonged survival (Ader, 1985). Because cyclophosphamide is quite toxic, as are many chemotherapeutic agents, this sort of use of conditioned immune change may be of considerable benefit. In more recent work (Grochowitz et al., 1991) it has also been suggested that conditioned immunosuppression can delay rejection of tissue transplants, suggesting a use in organ transplantation.

In more general terms, conditioned immunosuppression might be expected to occur whenever an organism repeatedly encounters an immunosuppressive agent in a particular environment. Chemotherapy for cancer is a particularly important example. Chemotherapeutic drugs are chosen for their ability to inhibit the cell division of rapidly replicating cells, among which are cancer cells. However, these agents also inhibit the replication of other rapidly dividing cells such as immune

cells. Thus chemotherapeutic agents are immunosuppressive. Indeed, cyclophosphamide is an often used drug for cancer chemotherapy. The repeated chemotherapy is typically done in the same room in the same hospital setting, and so conditioned immunosuppression might be expected to develop. Consistent with this argument, Bovjberg et al. (1990) found that women who had undergone a number of chemotherapeutic treatments for ovarian cancer displayed immunosuppression after simply being brought to the hospital prior to chemotherapy. This learned immune change could easily exacerbate the unconditioned effects of the drugs on the immune system, further compromising the ability of the patients to fight the cancer. The psychologist of learning could suggest many procedures that should reduce the conditioning (e.g., giving the chemotherapy in different environmental contexts, rather than always in the same context). Such work is currently under way.

Stress and Immunity

Much of the current interest in PNI stems from the possibility that exposure to environmental stressors might interfere with the immune response, thereby providing a potential link between stress and physical disease. Because stressors activate both the sympathetic nervous system and the hypothalamo–pituitary–adrenal axis (see Stanford & Salmon, 1993, for a recent comprehensive review), it is not surprising that stressors can impact on immunity. This is because, as noted earlier, plasma catecholamines released by sympathetic terminals and the adrenal medulla, as well as hormones released by the pituitary and the adrenal cortex, participate in the regulation of the immune response.

Indeed, numerous studies conducted over the past 30 or so years have demonstrated that a wide variety of stressors can alter many aspects of the immune response (see Solomon, 1969, for an excellent early example). In animals, acute exposure to electric shocks (Keller, Weiss, Schleifer, Miller, & Stein, 1983), social defeat (Fleshner, Laudenslager, Simons, & Maier, 1989; review by Bohus & Koolhaas, 1991), maternal separation (Coe, Rosenberg, & Levine, 1988; Laudenslager, Held, Boccia, Reite, & Cohen, 1990), rotation (Esterling & Rabin, 1987)), the odor of a stressed conspecific (Zalcman, Richter, & Anisman, 1989), immersion in cold water (Jiang, Morrow-Tesch, Beller, Levy, & Black, 1990), restraint (Bonneau, Sheridan, Feng, & Glaser, 1991a, 1991b), handling (Moynihan et al., 1990), intraperitoneal injection of saline (Moynihan, Koota, Brenner, Cohen, & Ader, 1989), and loud noise (Monjan & Collector, 1977) have all been shown to suppress some aspect of immunity. Chronic stressors such as crowding (Rabin, Lyte, Epstein, & Caggiula, 1987) have also been examined. Immune measures have ranged from effectors of cellular immunity, such as the development of cytotoxic T cells to an antigen, to effectors of humoral immunity, such as the development of antibody to an antigen, to nonspecifc measures, such as mitogenic stimulation of lymphocyte proliferation. The function of specific cell types, such as macrophages, has also been examined after exposure to a stressor (Zwilling et al., 1990), as has the secretion of soluble mediators such as the interleukins and the development of surface receptors for them (Weiss, Sundar, Becker, & Cierpial, 1989). Stressors have also been shown to alter the migration pattern of immune cells between and into compartments of the immune system such as spleen, thymus, and lymph nodes (Fleshner, Watkins, Bellgrau, Laudenslager, & Maier, 1992). Indeed, it is difficult to think of an aspect of immunity that has not been found to be altered by some stressor.

One question that psychologists often ask when presented with work such as this concerns whether the influence of stress on immunity merely reflects a simple physical impact of painful or arousing events or whether the interaction between stress and immunity embodies some of the more subtle aspects of psychological modulation of stress effects that can be observed in other areas of stress research. The answer is that the impact of stress on immunity cannot be explained in simple physical terms. As an example we chose some experiments from our own research. If several male rats are allowed to live together in a large enclosure, one will become dominant, that is, the alpha male. If a stranger is introduced into the environment, the alpha male will attack the intruder. The intruder begins by engaging in defensive aggression but invariably gives up and adopts species-typical defeat postures. Intruders never beat residents. Being placed into the established territory of the other rat, even for a brief period of time, severely inhibits the production of antibody to antigen administered before the intruder is introduced into the territory (Fleshner, Laudenslager, Simons, & Maier, 1989). This effect is all the more impressive when it is recognized that antibody is not measured until one to three weeks later. However, the important point is that it can be determined whether the inhibition of antibody is produced by the physical aspects of attack, such as being bitten or pushed, or the psychological factor of being defeated. This is because adopting and maintaining defeat postures tend to inhibit the attacks from the alpha male. That is, the two are negatively correlated. Thus one can ask whether it is engaging in submissive behaviors or being bitten and assaulted that is correlated with the reduction in antibody formation. It was the adoption of submissive behaviors—the correlation between time spent in defeat posture and antibody was −.80. Indeed, there were a small number of animals who did not submit at all and received numerous bites. Antibody in these animals was unaffected.

On the human level, acute stressors, such as final examinations (Dorian et al., 1982), battle task vigilance (Palmblad et al., 1976), and sleep deprivation (Palmblad, Petrini, Wasserman, & Akerstedt, 1979), have been shown to impact on immune parameters. More chronic conditions, such as divorce (Kiecolt-Glaser, Fisher, et al., 1987), bereavement (Schleifer, Keller, Camerino, Thornton, & Stein, 1983), and Alzheimer caregiving (Kiecolt-Glaser, Glaser, et al., 1987), also alter measures of immunity. The literature demonstrating these links has been the

subject of numerous recent reviews (Ader & Cohen, 1993; Cohen & Williamson, 1991; Weiner, 1991) and will not be reviewed here yet again. However, it should be emphasized that the study of the psychological modulation of immunity has only scratched the surface of the relationships that probably exist. Obviously, psychological factors cannot directly contact white blood cells and are capable of altering immunity because they modulate autonomic function and the release of peripheral hormones that modulate immunity. Thus any psychological event that alters these neural and hormonal factors is capable of modulating immunity. As an example, mood states such as depression are associated with dysregulation of the pituitary–adrenal system (Holsboer, Von Bardeleben, Gerken, Stalla, & Muller, 1984), and depressed individuals often have chronically elevated levels of glucocorticoids in blood (Carrol, 1978). As would therefore be expected, immune system dysfunction has often been reported to exist in depressed populations (Irwin, Daniels, Bloom, Smith, & Weiner, 1987; Schleifer et al., 1984). Emotions such as anger and anxiety might also be expected ultimately to impact on immunity (Fleshner et al., 1993). Indeed, thoughts ought to be capable of altering immunity. Thinking about or encountering a learned signal for an aversive or unpleasant event can activate autonomic outflow and the release of hormones and so are capable of impacting on immunity. For example, presentation of a previously neutral stimulus (a light, a tone, etc.) that has come to signal an aversive event can suppress a number of aspects of immunity (Lysle, Cunnick, Kucinski, Fowler, & Rabin, 1990).

This line of reasoning suggests more than the fact that emotions and thoughts impact on immunity. It further suggests that these effects will be subtle and selective. Stressors are not generic events that have identical peripheral outcomes. Different stressors produce different mixes of autonomic activation and hormones (Mason, 1971). For example, one stressor might lead to intense autonomic activation and consequent plasma catecholamine release but relatively little activation of the pituitary and adrenal glands and their hormones. Another might produce the opposite pattern. In addition, the time course of these changes will differ for different stressors, emotions, and thoughts. Moreover, personality, coping processes, and the like modulate the autonomic and hormonal consequences of exposure to stressors (Ursin & Olff, 1993). They too will then modulate the immune consequences of stressors (e.g., Mormede, Dantzer, Michaud, Kelly, & LeMoal, 1988). For example, the impact of final examinations depends on the student's level of loneliness (Kiecolt-Glaser et al., 1984), and the effects of divorce depend on the degree of prior attachment to the partner (Kiecolt-Glaser, Fisher, et al., 1987). This sort of modulation by psychological variables is not restricted to the effects of stress. For example, we noted earlier that repeated chemotherapeutic treatments result in conditioned immunosuppression to cues that regularly precede chemotherapy. However, this conditioning may be restricted to patients who are high in state anxiety, as measured in the hospital environment (Fredrikson, Furst, Lekander, Rotstein, & Blomgren, 1993). Thus different stressors and other psychological events that do impact on immunity may do so in different ways, producing different outcomes.

Yet another complexity stems from the fact that the specific immune response involves a complex cascade of events that extends over many days. The peripheral products of stress play numerous roles in regulating this cascade, and so the effects of stress will of necessity be variable. There will be conditions under which stressors interfere with immunity, have no effect, or even enhance immune measures (e.g., Croiset, Heijnen, Veldhuis, deWied, & Ballieux, 1987; Lysle, Cunnick, & Rabin, 1990; Lysle, Lyte, Fowler, & Rabin, 1987; Rinner, Schauenstein, Mangge, & Porta, 1992). The effects observed will depend on the precise blend, duration, and timing of hormones and sympathetic activation produced by the stressor. For example, Fleshner et al., 1992, and Zalcman, Minkiewicz-Janda, Richter, and Anisman, 1988, have found that a stressor will interfere with the production of antibody to an antigen (measured 1–3 weeks after antigen administration) only if stress occurs within narrow time ranges relative to antigen exposure. In addition, different aspects of the immune response are differently affected by autonomic function and hormones, and so the effects of a particular stressor on immunity might be quite selective, impacting on one kind of immunity but not on another. It is quite possible for a stressor to alter antibody generation, for example, but not alter T-cell proliferation (Maier & Laudenslager, 1988). Research exploring these sorts of interactions is in its infancy. However, efforts in these directions will doubtlessly uncover a rich matrix of psychological influence.

This discussion also leads to a caution. Not infrequently, investigators have drawn sweeping conclusions such as "stress suppresses immune function" from studies that have measured but one aspect of immunity at one point in time. This is akin to measuring a single aspect of neural function (e.g., the release of a single transmitter in a single nucleus) and making claims about what "stress does to the brain." Furthermore, these measures have often been nonspecific and assess some intermediate aspect of the immune response (e.g., production of interleukins, proliferation of cells in response to mitogens) rather than an effector endpoint that detects and clears antigen, recognizes and destroys tumors or virally infected cells, and so forth. The immune system contains a high degree of redundancy, and so the fact that an event might alter an intermediate product or step does not provide convincing information about whether the event in question would impact on a normal endpoint of the immune response (e.g., the production of antibody). Indeed, there are instances in which a condition influences one but not the other (Cunnick, Lysle, Armfield, & Rabin, 1991; Sheridan et al., 1991). It will take a considerable amount of research to distill the truly general principles from the specifics.

Implications for Disease

The popular press is replete with conclusions concerning stress-induced immunomodulation as the mechanism mediating between stress and disease. There is no question that stress can alter immunity and that stress can alter disease, but there is actually very little work directed at determining whether the effect on immunity is causal to the effect on disease. This is an issue because stressors can modulate many factors other than immunity that can impact on disease directly without intervention by the immune system. Some of these factors are biological. For example, numerous experiments have shown that exposure to a stressor can accelerate the growth of implanted tumors (Sklar & Anisman, 1981). The natural assumption has been that this is because the stressor impacted on immune processes involved in tumor control. However, stressors also alter blood flow, levels of hormones such as prolactin, body temperature, and so forth, all of which can directly affect the rate of growth of a tumor. In addition, human studies allow mediation by behavioral variables. Most chronic stressors (e.g., bereavement) doubtlessly change behavior patterns (e.g., eating, sleeping, drug intake, interaction with others), which can modulate the course of a tumor.

Clearly, careful analytic work is required to tie the impact of a stressor on disease to mediation by immunity. Fortunately, there are a small number of studies that do just that. An elegant example is provided by a series of studies conducted by Ben-Eliyahu, Yirmiya, Liebeskind, Taylor, and Gale, 1991. They worked with a tumor cell that is known to be very sensitive to regulation by natural killer (NK) cells. (NK cells are a type of lymphocyte that does not have to be activated for it to be able to destroy cells and responds in a relatively nonspecific way to a variety of tumor- and virally infected cells.) This gave them the advantage of knowing which aspect of immunity to measure. They implanted these tumor cells in rats and found that a stressor would exaggerate tumor growth and metastasis if it was given within 24 hours of tumor implantation. The stressor also reduced the ability of NK cells to kill tumor cells as measured directly in an assay. The question was then whether the effect on NK cells mediated the effect on tumor growth. Ben-Eliyahu et al. approached this question in two ways. First, they blocked the effect of the stressor on NK cells using a pharmacological agent that had no direct effect on the tumor. However, the agent blocked the effect of the stressor on the tumor. They then used an antibody directed against NK cells to produce the same change in NK activity that the stressor had produced, but without administering the stressor. This enhanced tumor growth. Thus the change in NK cells was both necessary and sufficient to produce the facilitation of tumor development. The same sort of conclusion can be drawn from work by Bonneau et al. (1991a, 1991b) using the herpes simplex virus. More work of this sort will be needed before we can make confident assertions about links to disease. Nevertheless, it is clear that stress can alter immunity and that this can exert major effects on disease. The next few years of research will determine the role of these links in human disease and will explore whether psychological interventions are capable of modifying the course of disease. A particularly promising study of this sort was reported by Fawzy et al. (1990). They found that cancer patients who received psychiatric group intervention showed an increase in NK cell activity, compared with untreated control participants. Furthermore, this change was correlated with changes in anxiety. Much more work like this is needed and is under way.

Connections From the Immune System to the Central Nervous System

Thus far we have been concerned with the influence of the CNS and psychological processes on immune function. We now turn to the other direction of influence in the bidirectional interactions between behavior and immunity—the impact of immune responses on brain and behavior. We begin with the immune-to-CNS link. The immune response occurs outside the nervous system in the periphery in response to peripheral antigen. For the brain to participate in the regulation of this response it must therefore receive information that an immune response is in fact occurring. Moreover, the generation of a specific immune response is a complex affair extending over a number of days and involving the interaction of many different cell types and mediators. Thus it might even be necessary for the CNS to receive detailed information about the course of the response. As would be expected, both the electrical and chemical activity of the brain do change as immune responses occur. For example, Besedovsky, Sorkin, Felix, and Haas (1977) found hypothalamic neural activity to increase at the time of peak B-cell proliferation to an administered antigen. Similarly, neurotransmitters in the hypothalamus, such as norepinephrine, also show profound changes at this time (Carlson, Felten, Livnat, & Felten, 1987). The antigen used in these experiments was a harmless protein, not an agent that produces illness or disease. Thus it was not illness or disease that altered neural activity; rather, the activity of the brain changed with the progress and course of an immune response per se.

How could this occur? After all, the cells of the immune system, such as T cells, B cells, and the like, have only limited access to the brain, because of the blood–brain barrier. This is a key question that has generated considerable excitement recently. Much of the focus has been on the soluble proteins released by immune cells, the cytokines, during the course of the immune response. These have always been thought of as messengers between cells of the immune system, but they may also converse with the nervous system. Space does not permit a discussion of the many cytokines; thus only one, interleukin-1 (IL-1), will be used as an example.

IL-1 is synthesized and secreted by a number of different cells. However, activated macrophages are the major source of IL-1 during the specific immune response. Macrophages are activated either by engulfing antigen or

by a number of chemical signals that bind to surface receptors on the macrophage. Activation of macrophages with virus or bacterial endotoxin produces a release of IL-1 and a subsequent alteration in the electrical activity of the brain (Saphier, 1992), as well as metabolism of the neurotransmitters norepinephrine, serotonin, and dopamine in a number of discrete brain regions (Dunn, Powell, & Small, 1989). These CNS changes to virus and endotoxin are known to be produced by IL-1, because an antagonist to the IL-1 receptor blocks them and the peripheral or central administration of IL-1 produces them (Dunn, 1993). Thus IL-1 and other cytokines may well be the communicators between the immune system and the brain, with potent effects on neural activity.

However, an interesting question remains. IL-1 and other cytokines are large lipophobic proteins and are therefore unlikely to readily cross the blood–brain barrier. Several possibilities have been proposed with regard to how cytokines could then alter neural activity. One is that there is an active transport mechanism to carry IL-1 across the barrier (Banks, Kastin, & Durham, 1989). Another is that IL-1 is able to cross the vascular endothelium in regions of the brain where the barrier is weak or absent, such as in the organum vasculosum lateralis terminalis (Katsuura, Arimura, Koves, & Gottchall, 1990). A final possibility is that IL-1 can stimulate peripheral nerves, such as the vagus, that send afferent input to the brain (Watkins et al., 1994). This suggests that the immune system may truly act as a sensory organ conveying information to the brain.

Immune Modulation of Behavior

The focus in PNI has been on psychological modulation of immunity. However, there are recent suggestions that events in the immune system can also modify behavior. Behavior, thoughts, and emotions vary across time in ways that often seem unpredictable. At the very least, psychological processes sometimes change, even though events in the external environment seem to have been constant. Internal events are doubtlessly responsible for some of these dynamics, and events in the immune system may well be a previously unsuspected part of this matrix.

The first hint of an immune-to-behavior causal link was provided by studies indicating that there is an increase in autonomic nervous system activity and the levels of pituitary–adrenal stress hormones in blood at various stages of an immune response to an antigen (Besedovsky, Sorkin, Keller, & Muller, 1975). That is, the occurrence of an immune response leads to the peripheral physiological equivalent of a stress response. In addition, the pituitary–adrenal response is activated by the same mechanisms that activate their response to stressors. The paraventricular nucleus of the hypothalamus is induced to release corticotrophin releasing factor into the portal blood; that is, the immune response communicates with the brain in order to release the peripheral stress hormones. The communication link is provided by IL-1 and perhaps other cytokines released by immune cells during the immune response (Berkenbosch, VanOers, Del Rey, Tilders, & Besedovsky, 1987). It is important to recognize that in these studies an immune response was elicited by administration of a harmless protein, not a pathogen. Thus it is the immune response itself that produced what appeared to be a stress response.

The foregoing description might suggest that behavioral manifestations of stress will appear at some stages of the immune response. Animal experiments support this contention. Animals exposed to fear or anxiety-arousing stimuli engage in a well-characterized set of behaviors including reductions in the following: activity, tendencies to explore novel objects, social interaction, food and water intake, and willingness to engage in sexual behavior. The administration of IL-1 or of substances that stimulate immune cells, such as macrophages, to release IL-1 produce all of these behavioral changes (Dantzer, Bluthé, Kent, & Goodall, 1993).

The behavioral effects of immune products are not limited to stress and stress-related behaviors. For example, we have recently begun to study potential relationships between immune processes and pain. The CNS contains circuitry that, when activated, enhances the pain that results from a painful stimulus, above and beyond that which the stimulus normally produces (see Coderre, Katz, Vaccarino, & Melzack, 1993, for a review). These mechanisms in the brain and spinal cord are especially important because they are thought to be involved in the production of chronic pain pathologies that create so much human misery. All of the studies of these neural mechanisms had activated them through direct electrical or chemical stimulation of the neurons involved. We wished to determine whether there were naturally occurring environmental events that would activate these neural hyperalgesia circuits. We reasoned backwards and asked whether there were circumstances under which it would be adaptive to experience exaggerated pain from a painful stimulus. It seemed to us that illness or injury might be such a condition. During these times it might be useful to be especially attentive to sites of pain. Pain could serve to guide recuperative behaviors, such as licking the site of injury (Bolles & Fanselow, 1980), and lead to the conservation of energy during illness (see below). We conducted a series of experiments in which rats were made ill by administering agents that induce illness, and in all cases a long-lasting hyperalgesic response to pain stimuli was induced (Wiertelak et al., 1994). This does not by itself implicate the immune system. However, in further studies we demonstrated that the hyperalgesia occurred because the illness-inducing agents stimulated macrophages to release IL-1 (Maier, Wiertelak, Martin, & Watkins, 1993) and that IL-1 did activate the hyperalgesia circuitry in the brain and spinal cord (Watkins et al., 1994). Note that injury as well as pathogenic agents will produce the release of cytokines such as IL-1 (see below).

We are unaware of comparable human studies. However, it would be intriguing to determine whether mood, emotional reactivity, pain, attention, and other processes might be affected by the status of the immune system, even when the immune system is merely re-

sponding to harmless as well as pathogenic agents that we all encounter in our daily experience. This could account for some of the seemingly unmotivated mood swings that we all experience.

Functional Significance—Inflammation and the Acute Phase Response

We next turn to a consideration of some of the "whys." Why would it be useful for stressors and other behavioral events to impact on immunity, and why should immune responding alter behavior? In particular, how could it be adaptive to interfere with the immune response? Is this simply pathophysiological or does stress-induced immunosuppression play a physiological role? Another way to inquire into this issue is to wonder why stress hormones are immunosuppressive. Conversely, why should immune responding produce what looks like a stress response?

Until now we have focused on the specific immune response. However, specific immunity is a more recent evolutionary development than innate immunity; it evolved from processes present in innate immunity. Indeed, specific immunity is present only in vertebrates (Reinisch & Litman, 1989). The stress response is far older in evolutionary time. Innate immune defenses are also quite old. For example, phagocytic cells that engulf and destroy particles are present in the sponges, the most primitive multicellular organism known. Thus an understanding of the physiological role of stress-induced immune changes might be illuminated by considering innate immunity and the role of stress.

Inflammation and the acute phase response (see Baumann & Gauldie, 1994, for a review) are particularly important aspects of innate immunity. These are innate or nonspecific because the cells involved do not respond only to a specific antigen or molecule but act on a broad range of substances. There is no antigen-driven multiplication of cells specific for an antigen.

Inflammation

Inflammation is a local response to tissue injury, microbial invasion or infection, and irritants. The purpose of the inflammatory response is to limit damage caused by injury to a local site. In the case of a pathogen, inflammation limits its spread and kills and removes the pathogen through phagocytosis, primarily by macrophages and neutrophils called to the site. In addition, inflammation involves the initiation of repair processes designed to fix any tissue damage. This involves proliferation of connective tissue, production of collagen and elastins, and so forth. The time course of these responses is on the order of hours—inflammatory responses can be observed within 1 to 2 hours after infection, and the acute phase response (see below) occurs 8 to 12 hours after local infection. Recall that the specific immune response requires days to generate effectors that can kill antigen. Thus inflammation and the acute phase response are the first line of defense against agents that have penetrated anatomic and physiological barriers.

Assume that a microbe enters the body or that tissue injury occurs. This activates a number of systems that ultimately lead a variety of cells to migrate to and enter the injured or affected area. The macrophage is perhaps the most important cell. Chemical signals that macrophages resident in the area receive from the initiating events in inflammation and signals that macrophages newly arrived in the area receive from resident macrophages activate the macrophages to produce a variety of products. Some are enzymes that help destroy pathogens and cellular debris produced by injury, and others regulate the activity of a number of other cells. Macrophages can also engulf and destroy microbes. An important point is that many macrophage products act back on the macrophage itself in a positive feedback fashion. For example, IL-1 released from macrophages stimulates IL-6 released from fibroblasts and macrophages themselves, which stimulates further IL-1 release. IL-1 can even induce itself, upregulating IL-1 gene transcription (Schindler, Bhezzi, & Dinarello, 1991). This is noted here because many macrophage products are highly dangerous and can kill healthy tissue as well as pathogens; proteases and lysosomal enzymes are examples. The message is that the inflammatory response has to be limited in some way because of the positive feedback properties involved.

The Acute Phase Response

The inflammatory process is localized at the site of injury or infection. It can trigger a general or systemic response, the acute phase response, that both supports the local reaction and fights infections that are no longer localized and have become systemic. Some of the support involves delivering more needed building blocks, such as amino acids, to the site of inflammation. Other aspects of the support involve the delivery of additional mediators, and still other aspects entail more global metabolic changes that facilitate the cellular processes of destruction of pathogen and repair of tissue, at the same time limiting pathogen growth. IL-1, IL-6, and tumor necrosis factor (TNF) produced by macrophages at the site are critical triggers of this acute phase response (Baumann & Gauldie, 1994). These products stimulate further cytokine release from local endothelial cells and fibroblasts, and when they accumulate in sufficient quantity they enter the circulation and orchestrate the elements of the acute phase response.

The acute phase response involves numerous processes. Leukocytes are produced in bone marrow and then enter the circulation and can migrate to the local site. In addition, a number of enzymatic reactions cause reductions in plasma iron and zinc, both of which are required for the growth of certain pathogens. Acute phase proteins are synthesized and released by the liver. These are a group of about 30 plasma proteins that play diverse roles, such as scavenging and removing cellular debris, promoting destruction of bacteria by activation of complement, for example. Importantly, fever is produced.

Fever is a phylogenetically old mechanism and is highly adaptive. Numerous experiments have demon-

strated that reducing fever by various means decreases survival after infection. The increased body temperature produced by fever accelerates a number of enzymatic reactions at the site of inflammation that operate suboptimally under normal circumstances because they can be damaging to healthy tissue, slows replication of microbes, and enhances the rate of proliferation of immune cells. It is important to understand that fever is not just an increase in body temperature. Rather, the set point for temperature is increased in hypothalamic temperature control centers by IL-1 action at the brain (Rothwell, 1992). Thus mechanisms to increase temperature are engaged that decrease temperature loss (e.g., peripheral vasoconstriction and huddling) and increase temperature production (e.g., muscular activity involved in shivering).

Energy Demand and Balance

All of this creates a tremendous energy demand. For example, it is estimated that each degree increase of body temperature requires from a 7% to a 13% increase in caloric energy production or metabolism, depending on the species and circumstances. Furthermore, the production of acute phase proteins and all of the cellular proliferation, production of cytokines, collagens, proteases, and so forth, require a large supply of amino acid building blocks. An energy demand of this magnitude requires changes that range from metabolism to behavior; this can only be coordinated by the CNS.

The cytokines, such as IL-1, IL-6, and TNF, may again be key coordinating elements, both peripherally and through their ability to communicate with the CNS. At the cellular level, IL-1 promotes the breakdown of muscle protein into amino acids (Baracos, Rodemann, Dinarello, & Goldberg, 1983), a process that is responsible for the muscle soreness experienced during infection. IL-1 also increases the availability of glucose for metabolism by peripheral tissues and the release of fatty acids from fat stores for similar use.

Recall that IL-1 and other cytokines produce a set of behavioral changes that are similar to those seen after stress: decreases in activity, exploration, social interaction, and food and water intake. Hyperalgesia was also discussed. All of these are also considered to be part of the acute phase response. Somnolence and increased slow wave sleep can be added to this set of changes. An examination of the list suggests that all of the behaviors are designed to reduce unnecessary energy expenditure, so that available energy stores can be used to fight infection or injury. Reductions in food and water intake might not make sense in this context, but consider that organisms in which these systems evolved must forage to find food and water and that digestion is energy intensive. Indeed, IL-1 and TNF slow digestion. Hyperalgesia should operate to reduce activity and direct behaviors such as licking to the site of inflammation. Increased sleep, particularly slow wave sleep, should reduce the brain's glucose demand, the brain being the body's major user of glucose.

In short, the intense energy demands of inflammation and the acute phase response may require a shift in the organism's entire energy balance, and this can only be accomplished by involving the CNS, so that the array of changes from metabolism to behavior can be orchestrated. This is another important reason why immune products must be able to communicate with the CNS. Again, IL-1, TNF, and IL-6 are key elements of the communication (Kent et al., 1992). Clearly, the suggestion is that the behavioral consequences of IL-1 and immune responding may function as behavioral energy conservation and may have evolved for that purpose.

Glucocorticoids

The level of adrenal glucocorticoids in blood rises sharply during inflammation and is considered part of the acute phase response. Again, cytokines released by macrophages and other cells are the mediators of the increased glucocorticoid synthesis and release from the adrenal cortex (Baumann & Gauldie, 1994). Similar to the sequence of events described above during the specific immune response, the cytokines appear to lead to a glucocortiocid response by acting at the hypothalamus, thus initiating a full hypothalamo–pituitary–adrenal response.

It is important to understand that the peripheral physiological action of glucocorticoids is to mobilize energy (Sapolsky, 1992). Glucocorticoids promote breakdown of muscle protein into amino acids, facilitate the conversion of amino acids and liver glycogen to glucose, antagonize the action of insulin (insulin stimulates glucose uptake into fat and muscle and suppresses liver glucose production), and enhance fat mobilization. In sum, glucocorticoids potentiate glucose increases while further breaking down protein. Here glucocorticoids and IL-1 operate in concert.

These actions produce the energy demanded by inflammation and the acute phase response. A final regulatory factor is required. Recall that a number of potentially destructive substances are released during inflammation and that there are positive feedback loops inherent in the biochemistry. Something must limit this process; an argument can be made that it is glucocorticoids. Glucocorticoids do inhibit or oppose a large number of the key mediators of inflammation. It should be obvious that IL-1, IL-6, and TNF are the key orchestrators of inflammation and the acute phase response, and glucocorticoids inhibit their synthesis at the genetic level (see Barnes & Adcock, 1993, for a review). In addition, glucocorticoids can interfere with the synthesis of receptors for these cytokines, thereby interfering with both the substances and the ability of cells to respond to them. Most or all of the other mediators of inflammation that were omitted from this review for simplicity are also inhibited by glucocorticoids (Barnes & Adcock). The conclusion is that glucocorticoids exert a strong counterregulatory effect on inflammatory processes. Consistent with this conclusion, numerous experiments have demonstrated that removal of the adrenal potentiates inflammation after infection and can lead to septic shock (Barnes & Adcock).

Indeed, one might wonder how inflammation and the acute phase response ever proceed, given that glu-

cocorticoids do rise. Obviously, the issue is one of balance between stimulatory and inhibitory forces. Glucocorticoids restrain; they do not prevent. In addition, glucocorticoids do not rise until a number of hours have passed and many of the early events have already taken place. The cytokines that stimulate glucocorticoids through an action at the brain have to accumulate in sufficient quantity to enter the circulation and ultimately alter neural activity. Finally, many of the actions of glucocorticoids are genomic and therefore require substantial periods of time to occur.

The Stress Response

We are now in a position to speculate about why stress impacts on immunity. The first question should be "What is a stress response, really?" It is really a fight–flight response, a set of changes that mobilize the organism for energy production. That is, it involves a shunting of energy toward muscular exertion and high levels of brain energy use (Sapolsky, 1992). As in the innate immune response, energy stores are mobilized but motor function is enhanced with increases in cardiac output due to increases in heart rate and contractile force and dilation of muscle arterioles, increasing blood supply to exercising muscles. In addition, the sensory side is enhanced—vigilance is induced, pupils are dilated for better distance vision, and so forth.

Although both the innate immune and fight–flight responses require energy mobilization, the energy must go to different places, and the behavioral requirements are completely different for the two responses. In fact, they are roughly opposite. During a fight–flight emergency it would not be useful for energy to be used to produce inflammation and the acute phase response; energy needs to go to the muscles and brain. It would not be adaptive to maintain fever, reduced activity, huddling, shivering, and somnolence. Hyperalgesia would not be adaptive, inasmuch as the organism would be likely to direct attention to sites of injury rather than engage in defense. Analgesia would be desirable, and that is what stress produces (Kelly, 1986). In short, except for the fact that both produce energy mobilization, inflammation and the stress response generally have opposite effects.

What this means is that during a fight–flight emergency it would be adaptive to produce energy and to inhibit inflammation and the acute phase response, should there be injury or infection during the encounter. Moreover, if the encounter is extended with periods of respite during which inflammation develops, it would be adaptive to reduce the innate immune response if the encounter starts again. There is something that does this—glucocorticoids. Therefore, during a fight–flight emergency it would be useful to produce glucocorticoids quickly, rather than several hours after the initiating event. This would produce energy and inhibit the inflammmatory response before it can develop, should there be injury. This is exactly what stressors do. Thus, when considering the innate response, there is a clear argument for an adaptive function of stress-induced immunosuppression.

It is possible to continue this line of argument by speculating about evolutionary considerations. The innate immune response is very old in evolutionary terms, probably older than the fight–flight response. Macrophages are extremely primitive cells. After all, defense against pathogens and tissue damage repair is required by even simple organisms. However, fight–flight can come into play only in an organism that has the sensory capacity to detect predators or other dangers, the motor capacity to make organized movements directed away from the danger or to damage the predator, and the integrative abilities to relate the two. Perhaps the fight–flight response evolved out of the inflammatory-response–acute-phase response machinery. Evolution works by using old parts for new purposes; organisms already had a system to defend against damage and infection. Energy was still needed, but it had to go to a different place, muscle and brain. A mechanism existed to produce energy and to reduce the energy demand made by inflammation and the acute phase response by inhibiting them, thereby allowing the energy to go to another area of demand such as muscle. All that was required was to move the glucocorticoid response forward in time. So, perhaps all that was needed was to initiate the hypothalamo–pituitary–adrenal response from a new source. Remember that macrophage-produced cytokines initiate the pituitary–adrenal response by acting at the hypothalamus. So, in the stress response it is initiated by neural input, rather than by peripheral cytokines.

You might also note that stressors, or events that elicit fight–flight, can bear a close resemblance to physical damage or events that produce physical damage. This concept goes back at least to Selye (1936), who viewed inflammation as a prototypical stressor. Interestingly, IL-1 and receptors for IL-1 are located in brain (Breder, Dinarello, & Saper, 1988; Takao, Tracey, Mitchell, & DeSouza, 1990). Perhaps physically challenging fight–flight stimuli activate the hypothalamo–pituitary–adrenal axis by activating brain IL-1. It is interesting to note that physical restraint activates messenger RNA for IL-1 in brain (Minami et al., 1991). Physical stressors might even be able to activate elements of the inflammatory response directly, thereby providing a pathway to brain. Perhaps more psychological stressors then evolved other pathways to activate the hypothalamo–pituitary–adrenal axis.

A final consideration is that the specific immune response evolved out of and uses many of the components of the innate immune system. Thus, stress-induced modulation of specific immunity might be a remnant of its effects on innate immunity. In fact, thinking of innate immunity and specific immunity as separate processes may be as misleading as thinking of cellular and humoral immunity as separate.

Conclusions

The major theme of this article is that the immune system and brain form a bidirectional interacting set of processes, each regulating the other. Psychological processes can influence this network and in turn be modulated by it. We

hope that we have provided some insight into the adaptive reasons why these links might exist and be sensible. These links provide great promise in terms of understanding health and disease, but as reviewed, a great deal of work needs to be done before strong conclusions are warranted. The issues involved are too important to allow sweeping conclusions at the present stage of knowledge.

It is our feeling that the next few years will be an exciting time in PNI research. Because PNI is a new field, the existing knowledge is, of necessity, first-order knowledge. Classical conditioning can modify immune processes, stress can alter immunity, and immune products can feed back and modulate behavior. However, the complexities, breadth, and richness of the interactions have yet to be elucidated. In addition, the details of the mechanisms involved are largely unknown. In the next few years, work of increasing sophistication at the behavioral, neural, and immunological levels should be accomplished.

PNI is one of the new emerging interdisciplinary fields being driven by the growing realization that systems cannot be understood in isolation. Simply studying immunology at the level of immune cells, neuroscience at the level of neurons, and psychology at the level of behavior cannot capture the complex interactions between levels. Living organisms are not composed of disconnected systems or processes. It is our conviction that progress waits at the interfaces between systems and levels. Comprehension of health and disease in particular awaits such analyses.

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