# Psychoneuroimmunology

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## Abstract

Psychoneuroimmunology is the study of the relationships among behavioral, neural and endocrine, and immune processes. Bidirectional pathways connect the brain and the immune system and provide the foundation for neural, endocrine, and behavioral effects on immunity. Examples of such effects are conditioned and stress-induced changes in immune function and in susceptibility to immunologically mediated diseases. These data indicate that researchers should no longer study the immune system as if it functioned independently of other systems in the body. Changes in immune function are hypothesized to mediate the effects of psychological factors on the development of some diseases, and research strategies for studying the clinical significance of behaviorally induced changes in immune function are suggested.

## Keywords

conditioning; immunity; stress

Once upon a time, the immune system was considered an autonomous agency of defense. Research conducted over the past 25 years, however, has provided incontrovertible evidence that the immune system is influenced by the brain and that behavior, the nervous system, and the endocrine system are influenced by the immune system. Psychoneuroimmunology, a new hybrid subspecialty at the intersection of psychology, immunology, and the neurosciences, studies these interactions (Ader, 1981b).

The immune system's defense of the organism against foreign, "nonself" material (antigens) is carried out by white blood cells, primarily T and B lymphocytes, that respond in various ways to the presence of antigens and retain a "memory" of encounters with them. Different immune processes can be distinguished by the particular cells that mount the body's defense. Antibody-mediated immunity refers to the production of antibodies by B cells derived from bone marrow; cell-mediated immunity refers to the actions of a variety of T cells derived from the thymus gland. Typically, immune defenses involve interactions among T and B cells and other specialized white blood cells (e.g., macrophages) and substances (cytokines) secreted by activated T cells. Not all immunity is based on the body's recognition of a previously encountered antigen, however. Natural killer (NK) cells, implicated in protection against the spread of cancer cells and the recognition of and defense against viruses, are a type of lymphocyte capable of reacting against some antigens without having had prior experience with them. A readily accessible overview of immune system functions is provided at the following Web site: rex.nci.nih.gov/PATIENTS/INFO_TEACHER/bookshelf/NIH_immune.





## BACKGROUND

Interactions between the brain and the immune system were first observed in the laboratory in the 1920s, when scientists found that immune reactions could be conditioned (Ader, 1981a). In the 1950s, there was a short-lived interest in the immunological effects of lesions and electrical stimulation of the brain. At the same time, research was initiated to study the effects of stressful life experiences on susceptibility to experimentally induced infectious diseases. Interest in this research was rejuvenated when, beginning in the 1970s, several independent lines of research provided verifiable evidence of interactions between the brain and the immune system.

We now know that the brain communicates with the immune system via the nervous system and neuroendocrine secretions from the pituitary. Lymphoid organs are innervated with nerve fibers that release a variety of chemical substances that influence immune responses. Lymphocytes bear receptors for a variety of hormones and are thereby responsive to these neural and endocrine signals. The best known of these signals are reflected in the anti-inflammatory and generally immunosuppressive effects of adrenocortical steroids (hormones released by the adrenal gland).

Lymphocytes activated by antigens are also capable of producing hormones and other chemical substances that the brain can detect. Thus, activation of the immune system is accompanied by changes in the nervous system and endocrine activity. Cytokines released by activated immune cells provide still another pathway through which the immune system communicates with the central nervous system (CNS). Although the precise site (or sites) at which cytokines act within the brain has not been identified, cytokines cause changes in the activity of the brain, in the endocrine system, and in behavior.

At the neural and endocrine levels, then, there is abundant evidence of interactions between the brain and the immune system. At the behavioral level, the most notable evidence of interactions between the CNS and immune system is the effects of conditioning and stressful life experiences on immune function. Another important line of research (not elaborated here) concerns the effects of immune processes on emotional states and other behaviors such as activity, sleep, and appetite.

## BEHAVIORAL INFLUENCES ON IMMUNE FUNCTION

Pavlovian conditioning of alterations of immune function provides the most dramatic illustration of a functional relationship between the brain and the immune system. In a prototypical study using a paradigm referred to as taste-aversion conditioning, animals consumed a novel saccharin solution, the conditioned stimulus (CS), shortly before they were injected with an immunosuppressive drug, the unconditioned stimulus (UCS). When all animals were subsequently injected with antigen, conditioned animals that were reexposed to the CS alone showed an aversion to it and an attenuated antibody response compared with conditioned animals that were not reexposed to the CS and nonconditioned animals that were exposed to saccharin (Ader & Cohen, 1975).

Studies have since documented the acquisition and extinction of conditioned nonspecific responses such as NK cell activity and various antibody- and cell-mediated immune responses (Ader & Cohen, 2001). Conditioning is not limited to changes associated with taste-aversion learning, and there is no consistent relationship between conditioned changes in behavior and conditioned changes in immune responses. Also, conditioned immunosuppressive responses cannot be ascribed to stress-induced or conditioned elevations of adrenal hormones. More recently, the conditioned enhancement, as opposed to suppression, of immune responses has been observed using antigens rather than pharmacologic agents as UCSs.

Data on conditioning in humans are limited. The anticipatory (conditioned) nausea that frequently precedes cancer chemotherapy is associated with anticipatory suppression of the capacity of lymphocytes to respond to foreign stimuli, and multiple sclerosis patients being treated with an immunosuppressive drug show a conditioned decrease in total white blood cell count in response to a sham treatment. Healthy subjects show enhanced NK cell activity when reexposed to a distinctive flavor previously paired with injections of adrenaline. In another study, it was shown that repeated injections of saline (which do not elicit an immune response) could attenuate the response to a subsequent injection of antigen. Conversely, however, repeated injections of antigen may not precipitate a reaction to a subsequent injection of saline.

Psychosocial factors, including stressful life experiences, are capable of influencing the onset or severity of a variety of immune disorders and infectious diseases. Such factors are also capable of influencing immune function. The death of a spouse, other "losses" (e.g., divorce), and other chronic stressors (e.g., caregiving for a chronically ill person)—and even less traumatic events such as school examinations—elicit distress and associated declines in immune function, including a depressed response to a viral antigen.

Clinical depression tends to be associated with some immunologically mediated diseases, and this fact has focused attention on the immunological effects of depression. Depressed patients show a decline in several measures of immunity, elevated antibody levels to herpes viruses, and a diminished ability to mount a specific cell-mediated response to varicella zoster virus, which is responsible for shingles (Herbert & Cohen, 1993). In none of these instances, however, has it been demonstrated that changes in immune function specifically cause the health effects of depression or other affective responses to stress.

Evidence documenting stress-induced alterations in immunity comes mostly from animal research. Early life experiences such as disruption of an animal's interactions with its mother, the social environment, exposure to predators, odors emitted by stressed conspecifics, and physical restraint or other noxious conditions induce neuroendocrine changes and modulate both antibody- and cell-mediated immunity. In general, stress suppresses immune function, but the direction, magnitude, and duration of the effects depend on the antigen, the nature of the stressful experience, and the temporal relationship between the stressful experience and the encounter with antigen. The effects of stress also depend on a variety of host factors, such as species, age, and gender.

The neural and endocrine changes presumed to underlie the immunological



effects of stressful life experiences have not been delineated. Any number of hormones or the patterning of hormonal responses could influence immunity. Elevated levels of adrenocortical steroids, the most common manifestation of the stress response, are generally immunosuppressive, and there are many stressor-induced changes in immune function that are mediated by adrenal hormones. However, many stress-induced changes in immunity are independent of adrenal activity.

The response to stressful life experiences involves complex interactions among behavior, the nervous system, the endocrine system, and immune response (Rabin, 1999). As a result, the literature on the immunological effects of stress has yielded some equivocal or seemingly inconsistent findings. It should not be surprising, though, that different stressors—commonly thought to elicit a common stress response—can have different effects on the same immune response. Also, one particular stressor can have different effects on different immune responses. Another source of variability may relate to the direct translation of procedures used in immunological research to behavioral studies. For example, a concentration of antigen that is optimal for the study of cellular processes or immunizations against disease may not be optimal for studies designed to investigate the psychobiological interactions that appear to influence immunoregulatory processes. Thus, for the latter purpose, we need studies in which antigen concentrations are at the lower levels to which individuals may be exposed in natural settings. Varying antigen dose would reduce the risk of masking the contribution of those biopsychosocial factors that influence health and illness in the real world.

If we are not always able to predict the direction, magnitude, or duration of the effects of stressful life experiences, it is clear nevertheless that stressful life experiences can influence immune functions; they can increase or decrease susceptibility to immunologically mediated diseases, permit an otherwise inconsequential exposure to some viruses to develop into clinical disease, or contribute to the reactivation of viral infections to which the individual was exposed in the past. Unfortunately, there are relatively few studies that have measured the relationship between susceptibility to a particular disease and those immune responses that are relevant to that disease.

## BIOLOGICAL IMPACT OF BEHAVIORALLY INDUCED ALTERATIONS OF IMMUNE FUNCTION

The effects of conditioning and of stressful experiences on immune function have been referred to as "small." The changes in immune function have remained within normal limits, and it is argued, therefore, that the effects of behavior on immune function have no clinical significance. Although there may be reason to question the selective application of the criterion of effect size, a concern for the biological impact of behaviorally induced changes in immune function is quite legitimate. The association between stressful life experiences and susceptibility to disease and the association between stressful life events and changes in immune function do not establish a causal chain linking stress, immune function, and disease. Thus, a central question that remains to be addressed concerns the biological (clinical) significance of behaviorally induced changes in immunity.

There is little, if any, human research in which an altered resistance to disease has been shown to be a direct result of changes in immune function induced by stressful life experiences. Animal studies of experimentally induced or spontaneously occurring diseases, however, are being developed to address this issue. Stressful stimulation delays the production of virus-specific antibodies in mice infected with influenza and suppresses NK cell activity and the development of some T lymphocytes in animals inoculated with herpes simplex virus (HSV). Although physical restraint is ineffective in reactivating HSV infections, disruption of the social hierarchy within a colony of mice increases aggressive behavior, activates the HPA axis,[2] and results in reactivation of HSV in a significant proportion of infected animals. When the spread of a lung tumor is related to NK cell function, several different stressors can decrease NK cell activity and increase lung disease.

Inflammatory processes, an essential component in the healing of wounds, can be modulated by the sympathetic nervous system and HPA axis. It is not surprising, then, that experimentally produced wounds heal more slowly in caretakers of Alzheimer's patients than in control subjects and in students tested before an examination rather than during summer vacation. Mice restrained for several days before and after they are wounded show a diminished inflammatory response, an elevated level of adrenocortical steroids, and a dramatic delay in healing.

Additional work with animals will enable studies of the mechanisms through which stressful life experiences affect health and determine whether disease susceptibility can, as hypothesized, be influenced by behaviorally induced alterations in immune function.

The biological impact of conditioning was examined using mice that spontaneously develop a disease similar to systemic lupus erythematosus in which there is an overreactivity of the immune system. In this case, a suppression of immunological reactivity would be in the biological interests of these animals. CS presentations without active drug were provided on 50% of the pharmacotherapy trials on which animals were scheduled to receive immunosuppressive drug. By capitalizing on conditioned immunosuppressive responses, it was possible to delay the onset of lupus using a cumulative amount of drug that was not, by itself, sufficient to alter progression of the autoimmune disease. Similarly, resistance to experimentally induced arthritis was achieved by exposing animals to a CS previously paired with immunosuppressive treatments. Among mice previously conditioned by pairing a CS with an immunosuppressive drug, reexposure to the CS following transplantation of foreign tissues delayed the immunologically induced rejection of the tissues. There is one clinical case study of a child with lupus who was successfully treated using a conditioning protocol to reduce the total amount of immunosuppressive drug usually prescribed. Although the effects of conditioning have been described as small, conditioned immunological effects can have a profound biological impact on the development of disorders resulting from an overreactive immune system, some cancers, and the survival of tissue transplants.

The issue of clinical significance has occasioned a lot of misplaced breast-beating and apologias in the name of scientific conservatism. Except, perhaps, for extreme and rare circumstances, the notion that a conditioned stimulus or



psychosocial conditions could, by themselves, perturb the immune system to an extent that exceeds normal boundaries and leads to overt disease is somewhat simplistic from either an immunological or a behavioral perspective. Given the complexity of the cellular interactions within the immune system and the interactions between the immune and nervous systems, a behaviorally induced deviation from baseline that did not exceed the normal boundaries would seem to be the only response that could reasonably be expected. As far as susceptibility to a particular disease is concerned, however, it would not be unreasonable to theorize that changes capable of altering immune responses relevant to disease could have clinical consequences when interacting with environmental pathogens or when superimposed upon existing pathology or an immune system compromised by host factors such as age or external influences such as immunosuppressive drugs of abuse. The potential importance of psychoneuroimmunological interactions, then, requires that we adopt research strategies that capitalize on individual differences; high-risk populations (e.g., the very young or old, people whose immune systems are compromised, those with genetic predispositions to particular diseases, those with existing disease); systematic variation of the magnitude of the antigen; and the measurement of responses that are demonstrably relevant to particular diseases.

## CONCLUSIONS

Psychoneuroimmunology is an interdisciplinary field that has developed and now prospers by ignoring the arbitrary and illusory boundaries of the biomedical sciences. As a result of the integrative research conducted in recent years, a paradigm shift is occurring; researchers can no longer study immunoregulatory processes as the independent activity of an autonomous immune system. These processes take place within a neuroendocrine environment that is sensitive to the individual's perception of and adaptive responses to events occurring in the external world.

Research predicated on the hypothesis that there is a single, integrated defense system could change the way we define and study certain diseases. Theoretically, it is likely that behavioral, neural, and endocrine interventions are relevant in the treatment of some immune system-related diseases (e.g., arthritis) and that immune system activity may contribute to the understanding and treatment of behavioral, neural, and endocrine disorders (e.g., depression or even schizophrenia).

We cannot yet detail the mechanisms mediating the effects of conditioning or stressful life experiences on immune responses, and further studies are needed. However, we do know that neural and endocrine changes are associated with changes in behavior and that there is a network of connections between the brain and the immune system. The existence of these bidirectional pathways reinforces the hypothesis that changes in the immune system constitute an important mechanism through which psychosocial factors could influence health and disease.

### Recommended Reading

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## Notes

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2. This term comes from the structures involved in the secretion of so-called stress hormones. During a stress response, the brain's hypothalamus (H) releases a chemical that affects the pituitary gland (P). The pituitary then secretes a hormone that causes the adrenal glands (A) to release corticosteroids (cortisol in humans, corticosterone in rodents) into the bloodstream.

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# Environmental and Behavioral Influences on Gene Activity

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## Abstract

The central dogma of molecular biology holds that "information" flows from the genes to the structure of the proteins that the genes bring about through the formula DNA → RNA → protein. In this view, a set of master genes activates the DNA necessary to produce the appropriate proteins that the organism needs during development. In contrast to this view, probabilistic epigenesis holds that necessarily there are signals from the internal and external environment that activate DNA to produce the appropriate proteins. To support this view, I review a substantial body of evidence showing that external environmental influences on gene activation are normally occurring events in a large variety of organisms, including humans. This demonstrates how genes and environments work together to produce functional organisms, thus extending the model of probabilistic epigenesis.

## Keywords

central dogma; probabilistic epigenesis; predetermined epigenesis

A virtual revolution that has taken place in our knowledge of environmental and behavioral influences on gene expression has not yet seeped into the social sciences in general and the behavioral sciences in particular. Earlier, it was not recognized that environmental and behavioral influences play an important role in triggering gene activity. Paradoxically, in biology there is an explicit dogma, formulated as such, that does not permit environmental influences on gene activity: the central dogma of molecular biology, first enunciated by Crick in 1958.

Although the central dogma may seem quite remote from psychology, I think it lies behind some psychological and behavioral theories that emphasize the sheerly endogenous (internal) development of the nervous system and early behavior (e.g., Elman et al., 1996) and the "innate foundation of the psyche" (e.g., Tooby & Cosmides, 1990), independent of experience or functional considerations. Such theories follow from the essentially dichotomous view that genes and other endogenous factors construct part of the organism and environment determines other features of the organism. The present essay is an attempt to show how genes and environment necessarily cooperate in the construction of organisms, and specifically, to show how genes require environmental and behavioral inputs to function appropriately during the normal course of individual development.

## THE CENTRAL DOGMA

The central dogma asserts that "information" flows in only one direction from the genes to the structure of the proteins that the genes bring about. The formula