The Mind-Body Interaction in Disease
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The brain and the immune system continuously signal each other, often along the same pathways, which may explain how state of mind influences health

The belief that the mind plays an important role in physical illness goes back to the earliest days of medicine. From the time of the ancient Greeks to the beginning of the 20th century, it was generally accepted by both physician and patient that the mind can affect the course of illness, and it seemed natural to apply this concept in medical treatments of disease. After the discovery of antibiotics, a new assumption arose that treatment of infectious or inflammatory disease requires only the elimination of the foreign organism or agent that triggers the illness. In the rush to discover antibiotics and drugs that cure specific infections and diseases, the fact that the body's own responses can influence susceptibility to disease and its course was largely ignored by medical researchers.

It is ironic that research into infectious and inflammatory disease first led 20th-century medicine to reject the idea that the mind influences physical illness, and now research in the same field — including the work of our laboratories and of our collaborators at the National Institutes of Health — is proving the contrary. New molecular and pharmacological tools have made it possible for us to identify the intricate network that exists between the immune system and the brain, a network that allows the two systems to signal each other continuously and rapidly. Chemicals produced by immune cells signal the brain, and the brain in turn sends chemical signals to restrain the immune system. These same chemical signals also affect behavior and the response to stress. Disruption of this communication network in any way, whether inherited or through drugs, toxic substances or surgery, exacerbates the diseases that these systems guard against: infectious, inflammatory, autoimmune, and associated mood disorders.

The clinical significance of these findings is likely to prove profound. They hold the promise of extending the range of therapeutic treatments available for various disorders, as drugs previously known to work primarily for nervous system problems are shown to be effective against immune maladies, and vice versa. They also help to substantiate the popularly held impression (still discounted in some medical circles) that our state of mind can influence how well we resist or recover from infectious or inflammatory diseases.

The brain's stress response system is activated in threatening situations. The immune system responds automatically to pathogens and foreign molecules. These two response systems are the body's principal means for maintaining an internal steady state called homeostasis. A substantial proportion of human cellular machinery is dedicated to maintaining it.

When homeostasis is disturbed or threatened, a repertoire of molecular, cellular and behavioral responses comes into play. These responses attempt to counteract the disturbing forces in order to reestablish a steady state. They can be specific to the foreign invader or a particular stress, or they can be generalized and nonspecific when the threat to homeostasis exceeds a certain threshold. The adaptive responses may themselves turn into stressors capable of producing disease. We are just beginning to understand the interdependence of the brain and the immune system, how they help to regulate and counterregulate each other and how they themselves can malfunction and produce disease.

The stress response promotes physiological and behavioral changes in threatening or taxing situations. For instance, when we are facing a potentially life-threatening situation, the brain's stress response goes into action to enhance our focused attention, our fear and our fight-or-flight response, while inhibiting behaviors, such as feeding, sex and sleep, that might lessen the chance of immediate survival. The stress response, however, must be regulated to be neither excessive nor suboptimal; otherwise, disorders of arousal, thought and feeling emerge.

The immune system's job is to bar foreign pathogens from the body and to recognize and destroy those that penetrate its shield. The immune system must also neutralize potentially dangerous toxins, facilitate repair of damaged or worn tissues, and dispose of abnormal cells. Its responses are so powerful that they require constant regulation to ensure that they are neither excessive nor indiscriminate and yet remain effective. When the immune system escapes regulation, autoimmune and inflammatory diseases or immune deficiency syndromes result.

The immune and central nervous systems appear, at first glance, to be organized in very different ways. The brain is usually regarded as a centralized command center, sending and receiving electrical signals along fixed pathways, much like a telephone network. In contrast, the immune system is decentralized, and its organs (spleen, lymph nodes, thymus and bone marrow) are located throughout the body. The classical view is that the immune system communicates by releasing immune cells into the bloodstream that travel to new locations to deliver their messages or to perform other functions.

The central nervous and immune systems, however, are more similar than different in their modes of receiving, recognizing and integrating various signals and in their structural design for accomplishing these tasks. Both the central nervous system and the immune system possess "sensory" elements, which receive information from the environment and other parts of the body, and "motor" elements, which carry out an appropriate response.

Cross Communication
Both systems also rely on chemical mediators for communication. Electrical signals along nerve pathways, for instance, are converted to chemical signals at the synapses between neurons. The chemical messengers produced by immune cells communicate not only with other parts of the immune system but also with the brain and nerves. Chemicals released by nerve cells can act as signals to immune cells. Hormones from the body travel to the brain in the bloodstream, and the brain itself makes hormones. Indeed, the brain is perhaps the most prolific endocrine organ in the body and produces many hormones that act both on the brain and on tissues throughout the body.

A key hormone shared by the central nervous and immune systems is corticotropin-releasing hormone (CRH); produced in the hypothalamus and several other brain regions, it unites the stress and immune responses. The hypothalamus releases CRH into a specialized bloodstream circuit that conveys the hormone to the pituitary gland, which lies just beneath the brain. CRH causes the pituitary to release adrenocorticotropin hormone (ACTH) into the bloodstream, which stimulates the adrenal glands to produce cortisol, the best-known stress hormone.

Cortisol is a steroid hormone that increases the rate and strength of heart contractions, sensitizes blood vessels to the actions of norepinephrine (an adrenalinelike hormone) and affects many metabolic functions — actions that help the body meet a stressful situation. In addition, cortisol is a potent immunoregulator and anti-inflammatory agent. It plays a crucial role in preventing the immune system from overreacting to injuries and

damaging tissues. Furthermore, cortisol inhibits the release of CRH by the hypothalamus — which keeps this component of the stress response under control. Thus, CRH and cortisol directly link the body's brain-regulated stress response and its immune response.

CRH-secreting neurons of the hypothalamus send fibers to regions in the brain stem that help to regulate the sympathetic nervous system, as well as to another brain stem area called the locus ceruleus. The sympathetic nervous system, which mobilizes the body during stress, also innervates immune organs, such as the thymus, lymph nodes and spleen, and helps to control inflammatory responses throughout the body. Stimulation of the locus ceruleus leads to behavioral arousal, fear and enhanced vigilance.

Perhaps even more important for the induction of fear-related behaviors is the amygdala, where inputs from the sensory regions of the brain are charged as stressful or not. CRH-secreting neurons in the central nucleus of the amygdale send fibers to the hypothalamus, the locus ceruleus, and to other parts of the brain stem. These CRH secreting neurons are targets of messengers released by immune cells during an immune response. By recruiting the CRH-secreting neurons, the immune signals not only activate cortisol-mediated restraint of the immune response but also induce behaviors that assist in recovery from illness or injury. CRH-secreting neurons also have connections with hypothalamic regions that regulate food intake and reproductive behavior. In addition, other hormonal and nerve systems — such as the thyroid, growth and female sex hormones, and the sympathomedullary pathways (connections of the sympathetic nervous system and medulla) — influence interactions between the brain and the immune system.

Immune System Signals
The immune response is an elegant and finely tuned cascade of cellular events aimed at ridding the body of foreign substances, bacteria and viruses. One of the major discoveries of contemporary immunology is that white blood cells produce small proteins that indirectly coordinate the responses of other parts of the immune system to pathogens.

For example, the protein interleukin-1 (IL-1) is made by a type of white blood cell called a monocyte or macrophage. IL-1 stimulates another type of white blood cell, the lymphocyte, to produce interleukin-2 (IL-2), which in turn induces lymphocytes to develop into mature immune cells. Some mature lymphocytes, called plasma cells, make antibodies that fight infection, whereas others, the cytotoxic lymphocytes, kill viruses directly. Other interleukins mediate the activation of immune cells that are involved in allergic reactions.

The interleukins were originally named for what was considered to be their primary function: communication among ("inter-") the white blood cells ("leukins"). But interleukins also act as chemical signals among immune cells and many other types of cells and organs, including parts of the brain. Cytokines is the more general term for biological molecules that many different kinds of cells use to communicate. Each cytokine is a distinct protein molecule, encoded by a separate gene, that targets a particular cell type. A cytokine can either stimulate or inhibit a response depending on the presence of other cytokines or other stimuli and the current state of metabolic activity. This flexibility allows the immune system to take the most appropriate actions to stabilize the local cellular environment and to maintain homeostasis.

Cytokines from the body's immune system can send signals to the brain in several ways. Ordinarily, a "blood-brain barrier" shields the central nervous system from potentially dangerous molecules in the bloodstream. During inflammation or illness, however, this barrier becomes more permeable, and cytokines may be carried across into the brain with nutrients from the blood. Certain cytokines, on the other hand, readily pass through

leaky areas in the blood brain barrier at any time. But cytokines do not have to cross the blood-brain barrier to exert their effects. Cytokines can attach to their receptors in the lining of blood vessels in the brain and stimulate the release of secondary chemical signals in the brain tissue around the blood vessels.

Cytokines can also signal the brain via direct nerve routes, such as the vagus nerve, which innervates the heart, stomach, small intestine and other organs of the abdominal cavity. Injection of IL-1 into the abdominal cavity activates the nucleus of the tractus solitarius, the principal region of the brain stem for receipt of visceral sensory signals. Cutting the vagus nerve blocks activation of this brain nucleus by IL-1. Sending signals along nerve routes is the most rapid mechanism — on the order of milliseconds — by which cytokines signal the brain.

Activation of the brain by cytokines from the peripheral parts of the body induces behaviors of the stress response, such as anxiety and cautious avoidance, that keep an individual out of harm's way until full healing occurs. Anyone who has experienced lethargy and excess sleepiness during an illness will recognize this set of responses as "sickness behavior." Indeed, patients receiving cytokine treatment for immunosuppression in cancer and AIDS may experience symptoms of depression and even suicidality. These symptoms can be prevented by pretreatment with antidepressants.

Neurons and nonneuronal brain cells also produce cytokines. Cytokines in the brain regulate nerve cell growth and death and can be recruited by the immune system to stimulate the release of CRH. Some have proposed that brain cytokines may play a role in symptoms of depression in the absence of known sickness or infection. The IL-1 cytokine system in the brain is currently the best understood — all its components have been identified, including receptors and a naturally occurring antagonist that binds to IL-1 receptors without activating them. The anatomical and cellular locations of such cytokine circuitry are being mapped out in detail, and this knowledge will aid researchers in designing drugs that block or enhance the actions of such circuits and the functions they regulate.

Excessive amounts of cytokines in the brain can be toxic to nerves. In genetically engineered mice, inserted genes that overexpress cytokines produce neurotoxic effects. Some of the neurological symptoms of AIDS in humans may also be caused by overexpression of certain cytokines in the brain. High levels of IL-1 and other cytokines have been found in the brain tissue of patients living with AIDS, concentrated in areas around the giant macrophages that invade the patients' brain tissue. Immune factors, however, are not always toxic to neurons. Specific activated T lymphocytes play an important role in preventing neuronal cell death after injury. This discovery is leading to new approaches to treating and preventing paralysis following spinal cord injury.

Any disruption of communication between the brain and the immune system leads to greater susceptibility to inflammatory disease and, frequently, to increased immune complications. For instance, animals whose brain-immune communications have been disrupted (through surgery or drugs) are highly liable to lethal complications of inflammatory diseases and infectious diseases.

Susceptibility to inflammatory disease that is associated with genetically impaired stress response can be found across species — in rats, mice, chickens and, though the evidence is less direct, humans. For instance, the Lewis strain of rat is naturally prone to many inflammatory diseases because of a severe impairment of its HPA (for hypothalamus, pituitary and adrenal) axis, which greatly diminishes CRH secretion in response to stress. In contrast, the hyperresponsive HPA axis in the Fischer strain of rat provides it with a strong resistance to inflammatory disease.

Evidence of a causal link between an impaired stress response and susceptibility to inflammatory disease comes from pharmacological and surgical studies. Pharmacological intervention such as treatment with a drug that blocks cortisol receptors enhances autoimmune inflammatory disease. Injecting low doses of cortisol into disease-susceptible rats enhances their resistance to inflammation. Strong evidence comes from surgical intervention. Removal of the pituitary gland or the adrenal glands from rats that are normally resistant to inflammatory disease renders them highly susceptible. Further proof comes from studies in which the transplantation of hypothalamic tissue from disease-resistant rats into the brain of susceptible rats improves their resistance to peripheral inflammation.

These animal studies demonstrate that disruption of the brain's stress response enhances the body's response to inflammatory disease, and reconstitution of the stress response reduces susceptibility to inflammation. One implication of these findings is that disruption of the brain-immune communication system by inflammatory, toxic or infectious agents could contribute to some of the variations in the course of the immune system's inflammatory response brain-immune communication system by inflammatory, toxic or infectious agents could contribute to some of the variations in the course of the immune system's inflammatory response.

CRH and Depression
Although the role of the stress response in inflammatory disease in humans is more difficult to prove, there is growing evidence that a wide variety of such diseases are associated with impairment of the HPA axis and lower levels of CRH secretion, which ultimately results in a hyperactive immune system. Furthermore, patients with a mood disorder called atypical depression also have a blunted stress response and impaired CRH function, which leads to lethargy, fatigue, increased sleep and increased eating that often results in weight gain.

Patients with other illnesses characterized by lethargy and fatigue, such as chronic fatigue syndrome, fibromyalgia and seasonal affective disorder (SAD), exhibit features of both depression and a hyperactive immune system. A person with chronic fatigue syndrome classically manifests debilitating lethargy or fatigue lasting six months or longer with no demonstrable medical cause, as well as feverishness, aches in joints and muscles, allergic symptoms and higher levels of antibodies to a variety of viral antigens (including Epstein-Barr virus).

Patients with fibromyalgia suffer from muscle aches, joint pains and sleep abnormalities, symptoms similar to early, mild rheumatoid arthritis. Both these illnesses are associated with a fatigue like that in atypical depression. SAD, which usually occurs in winter, is typified by lethargy, fatigue, increased food intake and increased sleep, symptoms similar to those of atypical depression.

A deficiency of CRH could contribute to lethargy in patients with chronic fatigue syndrome. Injection of CRH into these patients causes a delayed and blunted ACTH secretion by the HPA axis. That same response is also seen in patients whose hypothalamus has been injured or who have a tumor. Also, fatigue and hyperactivity of the immune response are associated with cortisol deficiency, which occurs when CRH secretion decreases. The hormone levels and responses in patients with fatigue syndromes suggest — but do not prove — that their HPA axis functions are impaired, resulting in a decrease in CRH and cortisol secretion and an increase in immune system activity. Together these findings indicate that human illness characterized by fatigue and hyperimmunity could possibly be treated by drugs that mimic CRH actions in the brain.

In contrast, the classic form of depression, melancholia, is actually not a state of inactivation and suppression of

thought and feeling; rather it presents as an organized state of anxiety. The anxiety of melancholia is chiefly about the self. Melancholic patients feel impoverished and defective and often express hopelessness about the prospects for their unworthy selves in either love or work. The anxious hyperarousal of melancholic patients also manifests as a pervasive sense of vulnerability.

Melancholic patients also show behavioral alterations suggestive of physiological hyperarousal. They characteristically suffer from insomnia (usually early-morning awakening) and experience inhibition of eating, sexual activity and menstruation. One of the most widely found biological abnormalities in patients with melancholia is that of sustained hypersecretion of cortisol.

Many studies have been conducted on patients with major depression to determine whether the excessive level of cortisol associated with depression correlates with suppressed immune responses. Some have found a correlation between hypercortisolism and immunosuppression; others have not. Because depression can have a variety of mental and biochemical causes, only some depressed patients may be immunosuppressed.

The excessive secretion of cortisol in melancholic patients is predominantly the result of hypersecretion of CRH, caused by a defect in or above the hypothalamus. Thus, the clinical and biochemical manifestations of melancholia reflect a generalized stress response that has escaped the usual counterregulation, remaining stuck in the "on" position.

The effects of tricyclic antidepressant drugs on components of the stress response support the concept that melancholia is associated with a chronic stress response. In rats, regular, but not acute, administration of the tricyclic antidepressant imipramine significantly lowers the levels of CRH precursors in the hypothalamus. Imipramine given for two months to healthy people with normal cortisol levels causes a gradual and sustained decrease in CRH secretion and other HPA axis functions, indicating that down-regulation of important components of the stress response is an intrinsic effect of imipramine.

Depression is also associated with inflammatory disease. About 20 percent of patients with rheumatoid arthritis develop clinical depression. A questionnaire commonly used by clinicians to diagnose depression contains about a dozen questions that are almost always answered affirmatively by patients with arthritis.

In the past, the association between an inflammatory disease and stress was considered by doctors to be secondary to the chronic pain and debilitation of the disease. The recent discovery of the common underpinning of the immune and stress responses may provide an explanation of why a patient can be susceptible to both inflammatory disease and depression. The hormonal dysregulation that underlies both inflammatory disease and depression can lead to either illness, depending on whether the perturbing stimulus is pro-inflammatory or psychologically stressful. That may explain why the waxing and waning of depression in arthritic patients does not always coincide with inflammatory flare-ups.

The popular belief that stress exacerbates inflammatory illness and that relaxation or removal of stress ameliorates it may indeed have a basis in fact. The interactions of the stress and immune systems and the hormonal responses they have in common could explain how conscious attempts to tone down responsivity to stress could affect immune responses.

Genetic Factors

How much of the responsivity to stress is genetically determined and how much can be consciously controlled is not known. The set point of the stress response is to some extent genetically determined. In addition, factors in early development, learning, and later experiences contribute to differences in stress responsiveness. An event that is physiologically highly stressful to one individual may be much less so to another, depending on the sum of each person's genetic tendency to hormonal reactivity and their previous experience. The degree to which stress could precipitate or exacerbate disease would then depend not only on the intensity and duration of the stressful stimulus but also on the person's learned perception of the event as stressful and on the set point of the stress system.

Psychological stress can affect an individual's susceptibility to infectious diseases. The regulation of the immune system by the neurohormonal stress system provides a biological basis for understanding how stress might affect these diseases. Thus, stress hormones released from the brain, cortisol from the adrenal glands, and nerve chemicals released from nerve endings (adrenalinlike molecules norepinephrine and epinephrine) all modify the ability of immune cells to fight infectious agents and foreign molecules.

There is evidence that stress does affect human immune responses to viruses and bacteria. In studies with volunteers given a standard dose of the common cold virus (rhinovirus), individuals who are simultaneously exposed to stress show more viral particles and produce more mucus than do nonstressed individuals. Medical students receiving hepatitis vaccination during their final exams do not develop full protection against hepatitis. These findings have important implications for public health. People who are vaccinated during periods of stress might be less likely to develop full antibody protection. Chronic stress also prolongs wound healing.

New research shows that at physiological concentrations and under certain conditions the stress hormone cortisol not only is immunosuppressive but also may enhance certain aspects of immune function. Furthermore, each part of the stress response — the brain-hormonal, the adrenalinlike nerve and the adrenal gland adrenalin — is regulated independently, depending on the nature of the stressful stimulus. This specific nature of the stress response explains how different kinds and patterns of stress affect illness differently. Therefore, whereas chronic stress is generally immunosuppressive, acute stress can enhance cell-mediated immunity and exacerbate contact dermatitis types of allergic skin reactions. Furthermore, animal studies show that social stress and physical stress have different effects on infection with different virus viruses, such as herpes and influenza virus.

Animal studies provide further evidence that stress affects the course and severity of viral illness, bacterial disease and septic shock. Stress in mice worsens the severity of influenza infection through both the HPA axis and the sympathetic nervous system. Animal studies suggest that neuroendocrine mechanisms could play a similar role in infections with other viruses, including HIV, and provide a mechanism for understanding clinical observations that stress may exacerbate the course of AIDS. Stress, through cortisol, increases the susceptibility of mice to infection with mycobacteria, the bacteria that causes tuberculosis. It has been shown that an intact HPA axis protects rats against the lethal septic effects of salmonella bacteria. Finally, new understanding of interactions of the immune and stress responses can help explain the puzzling observation that classic psychological conditioning of animals can influence their immune responses. For example, working with mice and rats, Robert Ader and Nicholas Cohen of the University of Rochester paired saccharin-flavored water with an immunosuppressive drug. Eventually the saccharin alone produced a decrease in immune function similar to that of the drug.

Social Stresses

Stress not only is personal but is perceived through the prism of social interactions. These interactions can either add to or lessen psychological stress and affect our hormonal responses to it, which in turn can alter immune responses. Thus, the social-psychological stresses that we experience can affect our susceptibility to inflammatory and infectious diseases as well as the course of these and other diseases. For instance, in humans, loneliness is associated with a "threat," or adrenalinlike pattern of activation of the stress response and high blood pressure, whereas exercising is associated with a "challenge" pattern of high blood flow and cardiac output. Studies have shown that people exposed to chronic social stresses for more than two months have increased susceptibility to the common cold.

Other studies have shown that the immune responses of long-term caregivers, such as spouses of Alzheimer's patients, become blunted. Immune responses during marital discord are also blunted in the spouse (usually the wife) who experiences the greatest amount of stress and feelings of helplessness. In such a scenario, studies have found that the levels of stress hormones are elevated in the affected spouse.

On the other hand, a positive supportive environment of extensive social networks or group psychotherapy can enhance immune response and resistance to disease — even cancer. Some studies have shown that women with breast cancer, for instance, who receive strong, positive social support during their illness have significantly longer life spans than women without such support.

For centuries, taking the cure at a mountain sanatorium or a hot-springs spa was the only available treatment for many chronic diseases. New understanding of the communication between the brain and immune system provides a physiological explanation of why such cures sometimes worked. Disruption of this communication network leads to an increase in susceptibility to disease and can worsen the course of the illness. Restoration of this communication system, whether through pharmacological agents or the relaxing effects of a spa, can be the first step on the road to recovery.

A corollary of these findings is that psychoactive drugs may be used to treat some inflammatory diseases, and drugs that affect the immune system may be useful in treating some psychiatric disorders. There is growing evidence that our view of ourselves and others, our style of handling stresses, and our genetic makeup can affect the immune system. Similarly, there is good evidence that diseases associated with chronic inflammation significantly affect one's mood or level of anxiety. Finally, these findings suggest that classification of illnesses into medical and psychiatric specialties, and the boundaries that have demarcated mind and body, are artificial.

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