CHAPTER 1

Psychoneuroimmunology: The Connection Between the Mind and the Body

Great men are they who see that spiritual force is stronger than any material force, that thoughts rule the world.

—Ralph Waldo Emerson

Learning Objectives

- Define psychoneuroimmunology.
- Understand the major historical milestones in the development of mind-body medicine.
- Define the role of and connection between the brain and the immune system.
- Understand the role of emotions and immunity in major diseases, such as heart disease and cancer.
- Understand the criticisms of mind-body medicine.
- Understand the challenges for mind-body medicine in the next century.

In a pronouncement that at first surprised the medical community, if not the lay public, one practitioner proclaimed that an estimated 90 percent of all physical problems have emotional roots. He followed up by saying that his estimate was, at best, conservative. A growing body of evidence now indicates that virtually every illness—from arthritis to migraine headaches, from the common cold to cancer—is influenced, for good or bad, by how we think and feel. Solid research is now confirming what many physicians have long observed: The state of the mind directly affects physical illness.[1]

There are compelling reasons to address the issue of disease beyond its personal effects. The global impact of physical illness is profound: In the United States alone, chronic disease costs hundreds of billions of dollars every year. In 2001, the United States spent $300 billion on cardiovascular disease, $100 billion on diabetes, and $117 billion on the costs associated with overweight people and obesity.[2]

As part of the effort to focus on prevention, seemingly disparate lines of research have converged into a new discipline of mind-body medicine that examines the relationship between the mind, the emotions, and the body. Mind-body medicine is based on the premise that mental and emotional processes (the mind) can affect physiological fnnction (the body), and a large body of evidence now supports this connection.[3]

Under the support of a National Institutes of Mental Health grant, physicians and researchers David Spiegel and Sara Stein write, "Once believed to be autonomously functioning mechanisms, the nervous, endocrine, and immune systems are now known to be integrally connected, with exquisitely sensitive communications and interactions."[4]

These and other researchers have shown that what we think and how we feel appear to have powerful effects on the biological functions of our bodies, especially on the immune system. It also shows that there is a complex, dynamic interaction between the mind and the body. Finally, it opens the revolutionary possibility that we can work with our physicians hy virtne of our attitudes and onr emotions, nnt just our biological systems.

A Definition

The scientific investigation of how the hrain affects the body's immune cells and how the immnne system can be affected by behavior is called *psychoneuroimmunology,* a term coined in 1964 by Dr. Robert Ader, director of the division of behavioral and psychosocial medicine at New York's University of Rochester. In their landmark stndy, Ader and his colleagues showed that immnne fnnction could be classically conditioned.[5] The science of psychoneuroimmnnology (PNI) focuses on the interaction between the mind, the brain, the nervons system, and the immune system. PNI investigates the relationship between psychosocial factors, the central nervons system, the immune system, and disease.[6]

As a science, PNI receives the endorsement of the National Institutes of Health and the snpport of prominent researchers. Candace Pert, a psychopharmacologist with Maryland-based Peptide Research and a visiting professor with the Center for Molecular and Behavioral Neuroscience at Rutgers University, points ont that "separate disciplines make it difficult to make progress. I think we're moving toward a much more interdisciplinary way of looking at things."[7]

David L. Felten, professor of nenrobiology and anatomy at the University of Rochester School of Medicine in New York, agrees. "The field of psychoneuroimmunology, as a scientific discipline—and I'm not talking about people who hang crystals from their rear-view mirrors, I'm talking about hard-core research—is showing that the nervous system and the immnne system communicate with each other massively, extensively, and continuously," he says.[8]

Though there is still some skepticism about the concepts behind it, PNI researchers are proving that the way people think and feel influences the immnne system. Immnnologists, physiologists, psychiatrists, psychologists, and nenrobiologists "who have explored the murky boundary between mind and body now suspect that certain negative psychological states, bronght on by adversity or a chemical imbalance, actually canse the immune system to falter."[9] Some even go so far as to claim that positive attitudes, such as a feeling of control, may in some way "inoculate against disease and act as a valnable supplement to couventional medical care."

Psychonenroimmunologists focus on the link between the mind, the braiu, the nervons system, and the immune system, and though these links are solid, researchers are still not sure whether they *cause* disease or *influence* the development of disease. Because evidence is still being gathered from a host of long-term studies, most researchers warn against overenthusiastic interpretations of the findings. Nonetheless, they view the new field—whether it goes by the name of *psychoneuroimmunology* or simply *behavioral medicine*—as the hottest and most promising area of medical research today.[10]

The evidence for such a link has accelerated remarkably in the past few years. An article in *Time*[11] cited some examples: A ten-year follow-up stndy at Stanford University showed that women who were ill aud received psychotherapy in groups survived nearly twice as long as similar women who didn't. Dr. Dean Ornish of the Preventive Medicine Research Institute in California showed that a mind-body program can reverse even severe coronary artery blockage after only a year, and he says the program may prevent it as well. Other studies have enabled researchers to predict which people in a group will become ill—based on nothing more than psychological profiles.

In yet another example of the growing body of evidence supporting the link betweeu mind and body, the late Norman Cousins, formerly the editor of the *Saturday Review* and a member of the UCLA medical faculty, twice intrigned both the medical commnnity and the public by overcoming usually fatal conditions—one, a massive heart attack, and another, au advanced case of ankylosing spondylitis (a degenerative spinal disease). Cousins followed his physicians' regimen each time, but also infused himself with vast doses of positive emotions and laughter. According to Cousins himself, he was healed not only by the miracle of modern medicine but also by the healing emotions of love, hope, faith, confideuce, and a tremendous will to live. Because of his experiences, both with his own illness and with the hundreds of patients he saw, he became an acknowledged authority on the power of emotion. Cousins's belief that emotion plays a profound part in bringing on disease and helping to combat it is not his alone.

A Brief History

The concept of and controversy surrounding the effect of emotions and stress on health are not new; the relationship between physical and psychosocial well-being has existed throughout history and across cultures.[12] More than 4,000 years ago, Chinese physicians noted that physical illness often followed episodes of frustration. Egyptian physicians of the same period prescribed good cheer and an optimistic attitude as ways to avoid poor health. Half a millennium before the birth of Christ, Hippocrates, considered the father of medicine, cautioned physicians that curing a patient required a knowledge of the "whole of things," of mind as well as body. That philosophy persisted for hundreds of years. In one of the best-known examples, the Greek physician Galen observed during the second century A.D. that melancholic women were much more prone to breast cancer than women who were cheerful.

In 600 A.D. in India, a well-regarded compilation of texts called the *Astangahradaya Sustrasthana* demonstrated a strong relationship between mental state and disease. The texts counseled physicians to "reject" patients who were "violent, afflicted with great grief, or full of fear." Further, it gave a poor prognosis to patients who were afflicted by intensely negative emotions. The texts warned that emotions such as hatred, violence, grief, and ingratitude are stronger than the body's capability for healthy balance, and those patients who could not abandon their negative emotions create new diseases as fast as a physician can heal an old one.

However, the suggested relationship between mental state and disease has not gone unchallenged. In the seventeenth century, the musings of philosopher-scientist René Descartes had a dramatic impact on the "holistic" attitude and philosophy of medicine. Descartes hypothesized that there were two separate substances in the world: matter, which behaved according to physical laws, and spirit, which was dimensionless and immaterial. The body was material, and the mind spiritual. His notion of a fundamental, unbridgeable chasm between the body and the spirit—between the brain and the mind—came to dominate not only medical philosophy but religious philosophy as well.

Research supported Descartes's theory, as it gained momentum throughout the beginning of the twentieth century. Robert Koch, a German country doctor, found that germs cause anthrax in sheep; this became one of the most significant medical discoveries of the time. In crude experiments, he recovered the anthrax germs from dying sheep, injected them into healthy sheep, and then watched those healthy sheep sicken and die of anthrax.

Since anthrax germs caused only anthrax disease, and no other disease, Koch theorized that every disease had a simple, specific cause: germs. The most respected medical authority of the time, Rudolf Virchow, disagreed; he subscribed to the theory that germs undoubtedly play a role in disease, but that many other factors were involved such as environment, heredity, nutrition, psychological state, preexisting health, and stress. However, Koch held stubbornly to his view, and so did most other practitioners of his day.

American physiologist Walter Cannon conducted a series of experiments early in this century that provided physical proof that glands in the body respond to stress. His early experiments demonstrated the relationship between stress and the hypothalamus, pituitary, and adrenal glands, and Cannon established himself as a pioneer of the relationship between the body's response to stress and its physiological symptoms. Several decades later, Austrian-born physician Hans Selye conducted brilliant and sophisticated experiments that gave us what we now know as the "fight-or-flight response" to stress.[13]

It was not until the 1960s that researchers began studying the immune system in earnest. The first time PNI was referred to as a science was in a 1964 paper by G. F. Solomon entitled "Emotions, Immunity, and Disease."[14] The immune defense system proved to be so complex that researchers were overwhelmed with the task of unraveling its parts and functions.

In the next major milestone, Stanford University psychiatrist David Spiegel and psychotherapist Irvin Yalom led support groups in the 1970s for women with advanced stages of breast cancer. The groups used a form of therapy in which they expressed their emotions about their cancer; Spiegel and Yalom found that the women who participated in the group therapy survived twice as long as the women who didn't participate in the therapy. The research attracted substantial attention from the medical community.

Not until the 1980s did immunologists finally start looking at the growing evidence that there might be anatomical links between the brain, the nervous system, and the immune system. This body of evidence split into three areas of research:

- The interaction between the nervous system, the immune system, and the neuroendrocine system
- The psychosocial components that influence immunity and their effects on health and disease
- The influence of immunity on psychological disorders and behavior

It is important to note that data from the last two branches of research are much more difficult to gather and interpret, leading to frequent controversy about research findings.

Today, the broad spectrum of scientists who devote their time to the study of the brain-immune system link concentrates on how emotions work to either enhance or cripple immune response. The most extensive current research is focusing on the effects of stress and depression on immunity.

The Mind-Body Connection Today

As mentioned earlier in this chapter, the work of psychologist Robert Ader, whose key experiments laid the foundation for the field of mind-body research, gave the following evidence for connections between the mind, the immune system, and the nervous system:[15]

- The central nervous system is linked to both the bone marrow and the thymus (where immune system cells are produced) and to the spleen and lymph nodes, where such cells are stored.
- Scientists have found nerve endings in the tissues of the immune system. The lymphoid organs, such as the spleen, are thoroughly laced with nerve fibers.
- Changes in the brain and spinal cord affect how the immune system responds. That's not all: When researchers trigger an immune response in the body, there are changes in the way the brain and spinal cord function.
- Researchers have discovered that lymphocytes (important immune system cells) respond chemically to hormones and neurotransmitters, and that they can actually produce hormones and neurotransmitters. And receptors for neuromodulators and neurohormones have been found on the T lymphocytes.[16]
- Emotions trigger the release of hormones into the system—adrenaline, noradrenaline, endorphins, glucocorticoids, prolactin, and growth hormones, among others.
- Cells that are actively involved in an immune response produce substances that send signals to the central nervous system.
- The body's immune response can be influenced by stress; stress and other psychosocial factors can make the body more susceptible to infectious diseases (such as the common cold), autoimmune diseases (such as arthritis), or cancer.
- The body's immune response can be "trained," modified by the same kind of classical conditioning used in psychological experiments to train dogs.
- Immune function can be influenced and changed by psychoactive drugs, including alcohol, marijuana, cocaine, heroin, and nicotine.

- The research into the relationship between the mind and the body has dramatic implications for treatment.

The way that we recognize, define, speak about, and behave in relation to our emotions may be heavily influenced by cognition, culture, history, location, gender, and other individual factors. With that in mind, physicians and surgeons on the cutting edge of technology are coming to realize that emotions as we perceive them play an extremely powerful role in both sickness and health. Dr. Theodore Miller of the renowned cancer institution, Memorial Hospital in New York, urged his fellow cancer surgeons to follow his example and not operate on patients who are convinced they will not survive surgery. In an address to the Society of Surgical Oncology, Miller told the surgeons that these patients usually do die, despite a technically successful operation.[17]

At least part of the power of emotions on health is due to their effect on the immune system. Jonas Salk, developer of the first polio vaccine, concluded years of his own scientific research by saying that "the mind, in addition to medicine, has powers to turn the immune system around." That power is so great, says Salk, that he advocates a major clinical study of the effects of emotions on the body, requiring dozens of years, millions of dollars, and an enormous number of scientists and children. It would be worth the investment, he says, if the study showed us conclusively that children who were positive and in control thrived and stayed healthier than their peers. "The people who do such a study," he concludes, "will be the poets of biology."[18]

As a science, PNI is still considered to be in its infancy, but already a number of medical schools are integrating it into their curricula and a host of federal grants are underwriting increased research. Most important, conferences on immunology now include at least one seminar on the relationship between the brain and the immune system. An increasing number of physicians are acknowledging that how a patient thinks and feels can be a powerful determinant of physical health.

PNI: The Major Components

The Brain

Five hundred years before the birth of Christ, the Greeks knew the brain as a three-pound organ inside the head.[19] Hippocrates believed that its role was to cool the blood and secrete mucus, which then flowed down through the nose. Through crude clinical observation over the ensuing years, beliefs about the brain and its function changed. In the Middle Ages, scientists regarded the brain as the seat of the soul. And during our own century, our ability to measure and analyze the electrical activity of the brain has generated major advances in understanding its function.

What the Brain Is

The brain is a very privileged organ: It has a heart to supply it with blood, lungs to supply it with oxygen, intestines to supply it with nutrients, and kidneys to remove poisons from its environment. The most important part of our nervous system, it is the focal point of organization. For the body to survive, the nervous system, and particularly the brain, must be maintained; all other organs will sacrifice to keep the brain alive and functioning when the entire body is under severe stress.

By weight, 90 percent of the central nervous system is located inside the head in the form of the brain. A long extension of the brain, the spinal cord, descends down the back inside the spinal column. Nerves branch out to the sensory organs—the eyes, ears, and nose—from both the brain and the spinal cord. Nerves also branch out to the muscles, the skin, and all the organs of the body.

The brain itself is made up of nerve cells and nerve fibers. If you looked at a cross-section of the brain, you would see mostly gray matter (containing cells) and white matter (containing fibers surrounded by a fatty insulation called myelin). The fibers and nerves of the spinal cord, as well as those that branch out through the body, are also insulated with myelin; this insulation serves to isolate the nerve fibers so that electrical nerve impulses can't "short out."

Brain functions are modulated by **neuropeptides,** body chemicals that act directly on the nervous system—at least seventy have been identified, including endorphins (which regulate pain relief and happiness), enkephalins (which regulate pain relief), glucocorticoids (which regulate mood, sexual behavior, sleep, and food intake), and adrenaline (which regulates fear).[20] These neuropeptides alter behavior and mood, and they reside in various receptors.

The receptors are proteins with three-dimensional folding patterns that provide a site where cells of all types receive most of their information about what surrounds them. In essence, a signaling molecule (called a "ligand") fits into the receptor site and influences the behavior of the cells. These molecules, or ligands, can be free molecules (like hormones) or can be on the surface of other cells. When the molecules are located on the surface of other cells, the cells must come into actual contact in order for them to communicate.[21] The brain stem is rich with receptors, and certain types of receptors are also found on the cells of the central nervous system and the immune system.

The neurotransmitters are responsible for the direct transfer of signals from one cell to another through the receptors. The neuropeptides set the "tone" by altering how effective the transfer of signals is.

What the Brain Does

Simply stated, the brain masterminds nerve impulses that are carried throughout the body and sends information to various parts of the body. It controls voluntary processes such as the direction, strength, and coordination of muscle movements; the processes involved in smelling, touching, and seeing; and other processes over which you have conscious control. The brain also controls many automatic, vital functions in the body, such as breathing, the rate of the heartbeat, digestion, bowels and bladder, blood pressure, and release of hormones.

Finally, the brain is the cognitive center of the body where ideas are generated, memory is stored, and emotions are experienced. The emotions that so affect the body originate in the brain, then, and this process explains the brain's powerful influence over the body as well as its link to the emotions and the immune system.

We are still learning about how the brain functions. For years, researchers believed that memories exist in the brain as fixed traces, carefully filed and stored. They taught that memory exists in a small seahorse-shaped section of the hippocampus and that other functions are centered in other localized areas of the brain. New research and a group of pioneering experts are now challenging that assumption.

In his book *The Invention of Memory: A New View of the Brain*, physician Israel Rosenfield presents the view that our brain is not "neatly and permanently wired up by our genes. Rather, whatever connections between nerve cells (neurons) we started with are continually reshaped by our experiences. It's a Darwinian struggle up there, and only the fittest connections—the ones that help us survive in our particular environment—get strengthened. Because experiences and contexts differ for each person, so do the connections. And since the demands of our own life vary over time, so do the patterns of connections, as some win and some lose."[22]

The philosophy of these pioneering scientists is "a radical departure from the past: Instead of having fixed memories, we invent what we remember. That is, we recategorize what we've learned, depending on the situation. We're creative magicians: The rabbit we pull out of memory's hat is different from the rabbit that went in—and so is the hat."[23]

According to Rosenfield's theory, we constantly reshape what enters our brain and we constantly assign new meaning to it. Our memory, he says, is inexact and fragmentary. His theory has begun to gain support in the scientific community, and even those who cannot wholeheartedly endorse it still admit that previous, rigid philosophies about the brain may not be entirely correct. Even if the theory is only partly valid, it may help explain how the brain so readily interacts with the emotions it produces and how its effect works on the body. According to Rosenfield, "A mental life cannot be reduced to molecules. Human intelligence is not just knowing more, but reworking, recategorizing, and thus generalizing information in new and surprising ways."[24]

The experience of emotion, then, "has less to do with specific locations in the brain and more to do with the complicated circuitry that interconnects them and the patterns of nerve impulses that travel along them," according to new research. California neuroscientist Floyd Bloom sums it up when he compares the manufacture of emotion to a television set. "There are individual tubes," he points out, "and you can say what they do, but if you take even one tube out, the television doesn't work."[25]

Emotions Produced by the Brain

The emotions produced by the brain are, in a very real sense, a mixture of feelings and physical responses—and every time the brain manufactures an emotion throughout its loose network of lower brain structures and nerve pathways known as the limbic system, physical responses accompany those emotions. A report published in *U.S. News and World Report* presents a vivid picture of what happens as feelings and physical responses are combined:

> *Seeing a shadow flit across your path in a dimly lit parking lot will trigger a complex series of events. First, sensory receptors in the retina of your eye detect the shadow and instantly translate it into chemical signals that race to your brain. Different parts of the limbic system and higher brain centers debate the shadow's importance. What is it? Have we encountered something like this before? Is it dangerous? Meanwhile, signals sent by the hypothalamus to the pituitary gland trigger a flood of hormones alerting various parts of your body to the possibility of danger, and producing the response called "fight or flight": Rapid pulse, rising blood pressure, dilated pupils, and other physiological shifts that prepare you for action. Hormone signals are carried through the blood, a much slower route than nerve pathways. So even after the danger is past—when your brain decides that the shadow is a cat's, not a mugger's—it takes a few minutes for everything to return to normal.*[26]

This description tracks what happens with fear, a relatively uncomplicated emotion. According to brain researchers, the pathways of more complicated sensations, such as sadness or joy, are much more difficult to trace, but they are just as responsible for physical effects in the body.

Chemicals Produced by the Brain

Endorphins. The brain manufactures natural, morphine-like chemicals called endorphins; the word *endorphin* itself is a derivative of the term *endogenous morphines*. Endorphins work as the brain's natural painkiller, sometimes exerting analgesic effects more powerful than those of narcotic drugs; they also produce a sense of calm, happiness, and well-being (responsible for the well-known runner's high). The hot spot for endorphin receptors is the part of the brain known as the amygdala, or "pleasure center."

The role of endorphins is apparently much more complex than was originally thought. According to a report published in *Psychology Today*, endorphins play a role in "crying, laughing, thrills from music, acupuncture, placebos, stress, depression, chili peppers, compulsive gambling, aerobics, trauma, masochism, massage, labor and delivery, appetite, immunity, near-death experiences, and playing with pets."[27]

Scientists have also found that certain foods give people a "sensory hit" and stimulate the release of endorphins. The result is a "feel good all over" experience that causes us to relate pleasure with food. The main food is sugary sweets. Johns Hopkins psychologist Elliott Blass has found that giving a sugar solution to rats under stress calms them in the same way that administering morphine does. But when the rats are given a drug that blocks the release of endorphins, the sugary solution no longer has a calming effect.[28]

Can there be a downside to all this ecstasy? Apparently so. In moderate amounts, endorphins can produce calm, inspire happiness, kill pain, and give us the thrill of anticipation over a warm-from-the-oven slice of spicy apple pie. But when too many endorphins are released by the brain, the effect can be devastating to the immune system.

According to research conducted at UCLA, a flood of endorphins released in response to pain or stress can bind to the natural killer cells, immune system cells that search out and destroy tumor cells. When endorphins bind to the natural killer cells, they falter and become less effective in their role as the body's "surveillance system"; the immune system may not detect and subsequently destroy invaders.

Peptides. Some of the most exciting brain-body research focuses on peptides, the body's natural chemical messengers. Pioneered by neuropharmacologist Candace Pert, peptide research studies the hormones that govern communication between the brain and the body cells. "There's probably a peptide solution to every medical problem," she says.[29] A band of researchers agrees with her—and believes peptide research may even hold the cure for Acquired Immunodeficiency Syndrome (AIDS).

Peptides are intercellular messengers that are widely distributed throughout the nervous system, the gastrointesrinal tract, and the pancreas.[30] "We have currently identified sixty to seventy, a number that may change rapidly as research advances, and they act like a sophisticated game of telephone played by the brain, the immune system, and the other organs and systems,"[31] says Joan Goldberg.

The Immune System

The immune system is a complex system consisting of about a trillion cells called lymphocytes, or white blood cells, and about a hundred million trillion molecules called antibodies. With these innate defenses, the immune system patrols and guards the body against attackers, both from the outside and from within. The most basic requirement of the immune system is that it can distinguish between "nonself" and "self" cells, and that it can then destroy the nonself invaders.[32] "Nonself" cells, or antigens, are unhealthy, dysfunctional, nonintegrated cells and tissues of the body, as well as foreign invading organisms such as bacteria and viruses. "Self" cells are the healthy, functional, integrated cells and tissues of the body. In destroying nonself cells, the immune system eliminates body cells and tissues that have become mutated or changed by disease or environmental factors.

Such action of the immune system is referred to as natural or innate immunity. Acquired immunity occurs when the immune system is exposed to a certain type of nonself cell. The next time an individual encounters the same antigen, the immune system is primed to destroy it. The degree of immunity depends on the kind of antigen, its amount, and how it enters the body. Infants are born with relatively weak immune responses, but they do get natural immunity during the first few months of life from antibodies they receive from their mothers. Children who are nursed receive even more antibodies through breast milk. In addition to acquiring immunity naturally, it is possible to be immunized with a vaccine. Vaccines contain microorganisms that have been altered so they produce an immune response but not full-blown disease.

According to Dr. Steven Locke, the associate director of Psychiatry Consultation Services at Beth Israel Hospital in Boston, the immune system does not operate within a biological vacuum but is sensitive to a number of outside influences. Locke sums up the role of the immune system as "a surveillance mechanism that protects the host from disease-causing microorganisms. It regulates susceptibility to cancers, infectious diseases, allergies, and autoimmune disorders."[33]

A variety of factors influence immunity and the immune system, including genetics, gender, age, and personality traits. When something goes awry in the immune system, infection results; when the entire immune system is compromised, as in AIDS, victims eventually die from overwhelming infections.

Lymphoid Organs

The organs of the immune system are spread throughout the body.[34] They are generally referred to as lymphoid organs because they are concerned with the growth, development, and deployment of lymphocytes, the key operatives of the immune system. Lymphoid organs include the bone marrow, thymus, lymph nodes, and spleen, as well as the tonsils, appendix, and clumps of lymphoid tissue in the small intestine known as Peyer's patches.

Cells destined to become lymphocytes are produced in the bone marrow cells in the hollow shafts of the long bones. Some of these cells, known as stem cells, migrate to the thymus, a multilobed organ that lies high behind the breastbone. Stem cells that mature in the thymus are called T cells; there, they multiply and mature into cells capable of producing an immune response. Other lymphocytes, which appear to mature either in the bone marrow itself or in lymphoid organs other than the thymus, are called B cells.

Lymph nodes are small bean-shaped structures distributed throughout the body in strings in the neck, armpits, abdomen, and groin, for instance. Each lymph node contains a variety of specialized compartments. Some house T cells; others, B cells. Still others are filled with another type of immunocompetent cell, macrophages, which are discussed in the next section. Lymph nodes also contain webbed areas that enmesh antigens. The lymph node brings together the various components that are needed to produce the body's immune response.

Lymph nodes are linked by a network of lymphatic vessels similar to blood vessels; they carry lymph, a clear fluid that bathes all of the body's tissues and that contains a variety of cells, most of them lymphocytes. Like a system of small creeks and streams that empty into progressively larger rivers, the vessels of the lymphatic network merge into increasingly larger tributaries. At the base of the neck, the large lymphatic ducts empty into the bloodstream.

Lymph and the cells and particles it carries, including antigens (cell-surface glycoproteins that the body recognizes as foreign) that have entered the body, drain out of the body's tissues, seeping through the thin walls of the smallest lymph vessels. As the lymph passes through lymph nodes, antigens are filtered out and more lymphocytes are picked up. The lymphocytes, along with other assorted cells of the immune system, are carried to the bloodstream, which delivers them to tissues throughout the body. The lymphocytes patrol everywhere for foreign antigens, then gradually drift back into the lymphatic system to begin the cycle all over again.

During their travels, circulating lymphocytes may spend several hours in the spleen, an organ in the abdomen that contains a high concentration of lymphocytes. Anyone whose spleen has been damaged by trauma or disease is very susceptible to infection.

The Immune System in Action

The immnne system stockpiles a tremendons arsenal of immunocompetent cells. By storing jnst a few cells specific for each potential invader, it has room for the entire array. When an antigen appears, these few specifically matched cells are stimulared to mnltiply into a full-scale army. Later, to prevent this army from proliferating wildly, like a cancer, powerful suppressor mechanisms come into play.

Lymphocytes are the white cells that bear the major responsibility for carrying ont the activities of the immnne system; the immnne system contains about a trillion of them. The two major classes of lymphocytes are the B cells and the T cells. The *B cells* secrete antibodies; each specific antibody exactly matches a specific invading antigen, mnch as a key fits a lock. These antibodies inactivate the antigens, rendering them incapable of causing disease. The body is capable of making antibodies to millions of antigens.

T cells do not secrete antibodies, but their help is essential for antibody production. The T cells act as both messengers and destroyers in the fight against pathogens. T cells ravage healthy cells from another person's body, which is why organ transplant recipients have problems with rejection. Some T cells become helper cells that tnrn on B cells or other T cells; others become snppressor cells that turn these cells off. Scientists believe there are as many as 100 million different varieties of T cells and another 100 million antibodies.

Natural killer cells are grannlar lymphocytes. As their name snggests, rhey attack and destroy other cells. They are called natural becanse they go into action without prior stimnlation by a specific antigen. Most normal cells are resistant to natural killer cell activity. Most tnmor cells, as well as normal cells infected with a virus, however, are snsceptible. Thus, the natural killer cell may play a key role in immnne surveillance against cancer, hnnting down cells that develop abnormal changes.

Macrophages and *monocytes* are large cells that act as scavengers, or phagocytes: They can engulf and digest maranding microorganisms and other antigenic particles. Monocytes circnlate in the blood, whereas macrophages are seeded throngh body tissues in a variety of gnises.

Macrophages play a crucial role in initiating the immune response by "presenting" antigens to T cells in a special way that allows the T cells to recognize them. In addition, macrophages and monocytes secrete an amazing array of powerfnl chemical snbstances called *monokines* that help to direct and regnlate the immnne respoose.

Granulocytes, like macrophages and monocytes, are phagocytes and thus are capable of enveloping and destroying invaders. They contain grannles filled with potent chemicals that enable them to digest microorganisms.

These chemicals also contribute to inflammatory reactions and are responsible for the symptoms of allergy.

Approximately twenty proteins circulate in the blood in inactive form and make up the immune system's complement system. The complement substances are triggered by antibodies that lock onto antigens; the result is often the redness, warmth, and swelling that occur with inflammation. They can also rapidly kill bacteria and other pathogens by puncturing their cell membranes.

Malfunctions

Fortunately, the immune system usually functions according to plan. Unfortunately, there are factors that can cause breakdown or failure of the immune system. For example, the immune system weakens as we age. With aging, the thymus shrinks: at age twenty it has lost approximately 75 percent of its size and function, and it is virtually gone by age sixty. The result is a significant change in the number and activity of T cells. Aging also upsets the ratio of helper to suppressor cells, resulting in turning off the immune response. Still another effect of aging is the production of antibodies by B cells.

The immune system can also be suppressed by cancer, and it can be damaged by the drugs and radiation therapy used to treat cancer. These treatments kill the rapidly growing cancer cells in the body, but can also destroy normal cells, especially those of the immune system.

The body can also develop a serious overreaction to substances that are usually harmless. In this malfunction of the immune system, there is a severe allergic reaction; the result can be a condition like asthma or anaphylactic shock.

A similar malfunction of the immune system is what researchers have termed *autoimmune disease*. The fine mechanisms of the immune system become unbalanced, and the immune system reacts to normal body tissues as though it were allergic to them. Simply stated, the body attacks itself. Many of these diseases are serious, progressive ones, such as rheumatoid arthritis and systemic lupus erythematosus, a disease in which the immune system mistakes the body's own tissues as the enemy, attacking and destroying them.

Cells of the immune system themselves may undergo malignant transformation, resulting in diseases such as lymphoma or leukemia. Finally, the immune system may be damaged or even destroyed by viral infections (such as AIDS) or congenital diseases that cause abnormalities in the immune system. Such immune system failures are called immunodeficiency diseases. When the immune system breaks down as a result of these diseases, the body is overwhelmed by infections and cancers because it can't destroy invading organisms.

We've known for years that disease can affect the immune system, but a more recent series of studies gives ample evidence that thoughts and emotions can also. Although a number of hormones and neurotransmitters can modulate the immune system, all of these are subservient to the emotions and beliefs of the individual.[35]

The Brain-Immune System Connection

The brain directs physiological processes in two ways: *neural*, communicating with cells through the nerves that innervate the glands and organs, and *endocrine*, stimulating the production of circulating hormones that then communicate with the cells.[36]

The connection between the brain and central nervous system and the immune system allows the mind to influence either susceptibility or resistance to disease. For example, the thymus gland plays an essential role in the maturation of immune system cells, and researchers have discovered extensive networks of nerve endings laced throughout the thymus gland.[37] Rich supplies of nerves also serve the spleen, bone marrow, and lymph nodes, giving further evidence of a link between the brain and the immune system.

Further, the cells of the immune system seem equipped to respond to chemical signals from the central nervous system. For example, the surface of the lymphocytes has been found to contain receptors for a variety of central nervous system chemical messengers,[38] such as catecholamines, prostaglandins, serotonin, endorphins, sex hormones, thyroid hormone, and growth hormone. National Institute of Mental Health researchers discovered that "certain white blood cells were equipped with the molecular equivalent of antennas tuned specifically to receive messages from the brain."[39] Macrophages and lymphocytes—themselves immune system cells—also produce hormones called *cytokines* that signal the brain in the same way as traditional hormones.[40]

More than three decades ago, Soviet researcher Elena Korneva discovered at the Institute of Experimental Medicine in Leningrad (now St. Petersburg) that she could produce changes in the immune system by selectively damaging different parts of the hypothalamus. Expanding on that theory, French researcher Gerard Renoux showed not only that the brain influences immunity, but also that different sides of the brain exercise different kinds of immunity. Renoux's brain experiments on mice show the profound influence of the brain—and the differing influences as well. When Renoux removed a third of the left side of the mouse's brain, the mouse could no longer respond with vigor to foreign material. When part of the right brain was removed, the number of **T** cells in the mouse's spleen was decreased.

Because of these receptors on the lymphocytes, physical and psychological stress alter the immune system. Stress has been shown to affect the T cells, B cells, natural killer cells, and lymphocytes. One of the most frequently implicated ways in which stress alters immunity, however, is by suppression of the natural killer cells, which could have important implications on cancer prognosis and the progression of HIV infection.[41]

Stress causes the body to release several powerful neurohormones—including catecholamines, corticosteroids, and endorphins—which bind with the receptors on the lymphocytes and alter immune function. Corticosteroids, in fact, have been found to have such a powerful influence in suppressing the immune system that they are widely used to treat allergic conditions (such as asthma and hay fever) and autoimmune disorders (such as rheumatoid arthritis and rejection of transplanted organs). These corticosteroids and other brain chemicals are unleashed by the hypothalamus, a section of the brain that is a virtual drug factory. The chemicals released by the hypothalamus have the most profound effects on the immune system.

The link between the mind and the immune system has gained a new dimension with the growing evidence that psychosocial factors directly affect immune function. The resulting findings have the potential of influencing a wide range of disorders, including allergies, infections, autoimmune diseases, and even cancer.

PNI research has demonstrated that our psychological, behavioral, and physical processes are closely integrated. Illnesses don't just happen: many are caused by bacteria, viruses, fungi, or other microbes. But what factors determine whether you will fall ill when exposed to these? What determines your immunity?

Part of immunity seems determined by emotions—how you think and feel. What is going on inside your mind, your heart, and your spirit may have tremendous impact on what happens to your body. In a thirty-year study of initially healthy young men, those with the most mature emotions and psychological style—including a sense of humor, an altruistic bent, and so on—were the healthiest thirty years later.[42] After thirty-five years, only 3 percent of those who dealt with the stresses of life in a mature, adaptive way had any chronic illness, as compared with the 38 percent who were either dead or chronically ill in the other group (who coped by using denial, blaming, repression, and intellectualization).

The result of this study supports the case for a new way of practicing medicine. There are several solid principles behind the notion of mind-body medicine. First, mind-body medicine appears to work through complex physiologic systems that are not normally under voluntary control.[43] For example, the production and release of natural opioids (painkillers) can be stimulated by hypnotic suggestion—and can be so powerful that patients can undergo surgery without the use of anesthesia. Biofeedback training can alter blood pressure, heart rate, and other vital signs. Meditation can bring about muscle relaxation, reduced heart rate, and slowed breathing. The physiological conditions that result from these types of mind-body medicine are directly opposite of the physical effects of stress—and work to promote, not impair, health.

The second principle behind mind-body medicine is that the peptides carry not only information about the nervous system and the body's physical functions, but also information about the emotions. That's not all: Information about the emotions is carried throughout the body, potentially impacting every body system.

The Immune System and Emotion

In reality, it may be too simplistic to say that emotions cause disease. More accurately, emotions are only one important factor in the body's ability to execute resistance mechanisms when it is exposed to causative factors. Normal homeostasis, the optimal balance of hormones, immunity, and nervous system functioning, protects us from the many threats to health we encounter daily. Disrupted emotional responses, and feeling "out of control," lead to disrupted homeostasis. Physiological processes then get out of control. Interestingly, the same part of the midbrain that controls most automatic homeostasis and keeps physiology balanced also controls emotional response, allowing responses to be "enough, but not too much."

There's a physiological reason why emotions can impact health. Different parts of the brain are associated not only with specific emotions, but also with specific hormone patterns. The experience ("release") of certain hormones, then, is associated with different emotional responses, and those hormones affect health.[44] As one example, we know that emotionally induced shifts in hormones can lead to chronic disease, such as high blood pressure. When a person is aggressive and anxious, too much norepinephrine and epinephrine are secreted, even at rest. The arteries thicken, and the excess hormones cause blood vessel muscles to constrict. The gradual rise in blood pressure can then result in hypertension, stroke, or heart failure.[45]

Other studies have borne similar results. It has long been believed, for instance, that as many as 70 percent of all people who go to a gastrointestinal specialist have irritable bowel syndrome, a mixture of pain, diarrhea, constipation, nausea, and sometimes vomiting. Most are women, and most have some kind of an emotional problem. One-fourth of gastroenterology patients have major depression.

One scientific study reported in the *Medical Journal of Australia* tested what would happen when irritable bowel syndrome patients received psychotherapy instead of conventional medical treatment for their condition. The result was that symptoms among the treated patients improved dramatically. After receiving counseling for their emotional upsets, 89 percent of the patients reported less pain as a result; 96 percent had less diarrhea, 90 percent had less constipation, 92 percent were less nauseated, and 81 percent had less vomiting. Researchers who conducted the study concluded that "the symptoms of irritable bowel syndrome were seen as a physical expression of emotions caused by recent loss or ongoing stressful life situations."[46]

Feeling these emotions is only one factor in the subsequent development of disease. Many researchers believe that the inability to express emotions is an even greater cause of disease. Studies have confirmed that the failure to perceive and express emotions can lead to various disease states.[47] Yale surgeon Bernie S. Siegel, well known for his humanistic work with cancer patients, put it this way:

> *Patients must be encouraged to express all their angers, resentments, hatred, and fears. These emotions are signs that we care to the utmost when our lives are threatened. Time after time, research has shown that people who give vent to their negative emotions survive adversity better than those who are emotionally constricted. Among patients with spinal-cord injuries, those who express strong grief and anger make more progress in rehabilitation than those with a more stoical attitude. Mothers who show great distress after giving birth to a deformed infant give the child better care than those who seem to take the misfortune calmly. In a study of people living near Three Mile Island, Dr. Andrew Baum found that those who showed their rage and fear suffered far less from stress and psychological problems than those who took a "rational" approach. Unexpressed feelings depress your immune response.*[48]

In a battery of tests conducted by Leonard Derogatis, it was found that breast cancer patients who showed little emotion were the ones who died early on. The "survivors" were the ones who felt and openly expressed a lot of anger, fear, depression, and guilt.[49] Apparently, the process of suppressing emotion contributed to the tenacity of the disease.

Infectious diseases—such as infectious hepatitis or gonorrhea—are caused by identifiable microorganisms such as bacteria or viruses. But emotions can even determine in part how susceptible we are to these infections agents, and whether they will actually make us sick.

An excellent example is the herpes simplex virus, which causes fever blisters and cold sores. Most adults harbor this virus in a quiescent state at all times. It often resides around the nostrils and the mouth but remains dormant and does not cause sores. Sometimes, in response to lowered resistance, it flares up, especially when the person is ill with something else (such as the common cold). Many times, it flares up in response to emotional upset. In fact, mental stress is the most common precipitant of herpes skin lesions.

A number of studies have demonstrated the power of emotions in bringing on an attack of herpes virus infection. In one, students who had a high prevalence of cold sores throughout college found that their cold sores occurred less frequently after graduation, when stress levels were lower.[50]

Medical officer Jerome M. Schneck at California's Fort MacArthur recalls a soldier who could accurately predict when his herpes simplex infection would become active. He knew that as soon as he felt hostile emotions, he could anticipate a breakout. He also learned that if he channeled his hostility into something else (such as reading), he was able to prevent the lesions from erupting.[51]

One of the reasons why strong negative emotions may be linked to illness is that negative emotional response, whether it be stress, anger, or sadness, may disrupt the immune system. When you experience strong emotions, your body responds much like it would in the classic "fight-or-flight" response model. Endocrine system activity sends hormones coursing through the bloodstream, which in turn send messages back to the nervous system. As the chemical response gradually builds, your body reaches its physical threshold and ability to deal with the stress of negative emotion; thus, one becomes more susceptible to illness.

Evidence also suggests that emotions send chemical messages to the brain; in response, the brain alters involuntary physiologic responses. The resulting alteration may affect the way the immune system responds to messages from the brain in the presence of disease.[52]

One of the most startling examples of how the mind can alter the immune response was discovered by accident. In 1975, Dr. Ader wanted to condition mice to avoid saccharin. He accomplished this by feeding the mice saccharin while simultaneously injecting a drug that caused upset stomach and that, incidentally, also suppressed the immune system. Associating the saccharin with the stomach pains, the mice soon learned to avoid the sweetener.

Ader then decided to try to reverse the taste aversion to saccharin. This time, Ader gave the same mice saccharin again, but without the drug that caused upset stomach. He was startled to find that the mice who had received the highest amounts of sweeteners during the initial conditioning died when they received saccharin alone. Ader speculated that he had so successfully conditioned the mice that saccharin alone now weakened their immune systems enough to kill them.[53] No previous research had documented a link between the mind and the immune system; until Ader's work, the two were assumed to work independently of each other.