IN JUNE 1985, THE NEW ENGLAND JOURNAL OF MEDICINE PUBLISHED A study about the effects of social and psychological factors on the course of cancer. The investigators had examined whether a range of psychological factors affected the medical outcome of patients with advanced tumors, and they had found no correlation. The study was later criticized on a number of counts. At the time, however, an accompanying editorial by an editor of the New England Journal took the opportunity to question the entire notion that the mind could have a demonstrable effect on health. The much-quoted editorial stated that "Most reports of such a connection are anecdotal," and concluded, "It is time to acknowledge that our belief in disease as a direct reflection of mental state is largely folklore."

Six years later, in the fall of 1991, the New England Journal published a watershed report showing a direct link between mental state and disease. That study demonstrated a striking correlation between levels of psychological stress and susceptibility to infection by a common-cold virus. The publication of such a study in the world's most respected medical journal marked a turning point in medical acceptance of the mind/body connection and, in particular, of the notion that stress and psychological factors could affect the function of the immune system.

Although the 1991 study didn't identify the physiological mechanisms

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A WHO'S WHO OF THE IMMUNE SYSTEM

The cells of the immune system form a multifaceted and powerful army. The key ones are the lymphocytes—small white blood cells that attack threats to the body in a number of ways.

B-lymphocytes, or B-cells—so named because they were first discovered, in chickens, in a gland called the bursa—are the cells that produce circulating antibodies. Antibodies, in turn, are tiny proteins—members of the family of proteins called immunoglobulins—that attack bacteria, viruses, and other foreign invaders (called antigens). Antibodies "fit" the molecules of the antigens they attack, much as a key fits a lock. Each antibody will attack only a single kind of antigen—one will go after a common-cold virus, for example, while another will attach to a bacterium that causes pneumonia—and each B-lymphocyte produces only one kind of antibody.

T-lymphocytes, or T-cells, don't produce antibodies. Instead, these cells themselves attack foreign invaders or work with other cells that do. (The T comes from the thymus gland, where these cells undergo much of their development.)

The several different groups of T-cells have different functions. Cytotoxic (cell-killing) T-cells, along with other blood cells called natural killer (NK) cells, constantly patrol the body, searching for dangerous rogue cells. Once they find them, these T-cells attach themselves to the invading cells and release microscopic packets of toxic chemicals that destroy them. Each cytotoxic T-cell, like each antibody, is "designed" to attack only a very specific target: Some attack cells that have been infected by viruses, some attack cancer cells, and some attack transplanted tissues and organs (to the frustration of transplant surgeons and their patients). Each NK cell, in contrast, has a broad range of targets and can attack both tumor cells and a wide variety of infectious microbes.

Two other classes of T-cells, called "helper" and "suppressor" T-cells, are especially important because of their overarching regulatory effects on immunity. Helper T-cells stimulate B-lymphocytes to produce antibodies, while suppressor T-cells shut off the helper T-cells when enough antibodies have been produced. These cells communicate with each other by producing interferons, interleukins, and other chemical messengers that govern the activity of immune system cells.

For optimal health, the helper/suppressor cell ratio should be in balance. People with AIDS and other immunodeficiency diseases have low ratios (too few helper cells); people with autoimmune diseases, characterized by an overactive immune system, often have high ratios.
SOME BACKGROUND: THE IMMUNOLOGICAL BASICS

The immune system is the body's means of defense against infectious disease and cancer. It has two primary tasks: to distinguish between “self” and “nonself,” and then to destroy, inactivate, or eliminate foreign substances that are identified as nonself—not naturally part of the body.

The two major arms of this protective complex are the humoral and the cellular immune systems. In the former, white blood cells called B-lymphocytes produce antibodies, proteins that are key to the body's defense against bacteria and viruses in body fluids. In contrast, the cellular immune response defends against cancer cells and viruses that have taken up residence inside the body's cells. (It's also the branch of the immune system that attacks transplanted tissue, and that has to be controlled to keep organ transplants from being rejected.)

The cellular immune response is not carried out by antibodies, but by various immune system cells. Among them are T-lymphocytes, which help organize the overall immune response; macrophages, which engulf and dissolve invading organisms; and natural killer (NK) cells, which defend against virus-infected cells and cancer.

Most recently, the AIDS epidemic has highlighted the importance of the immune system in maintaining health. The AIDS virus invades and destroys critical immune system cells, leaving the infected person open to a host of diseases that would be rebuffed by a normal immune system. But less severe immunological problems can also have an impact on health: A person with an underactive immune system will be especially susceptible to infections. Someone with an overactive immune system, one that cannot accurately distinguish between self and nonself, is at risk for allergies or autoimmune disease. And many experts believe that immune dysfunction can contribute to the development and spread of cancer.

DO SMALL STRESSES REALLY MATTER?

When PNI researchers first turned from rats to human beings, they began by examining the effects of very intense events on the immune response. For example, they found altered immune function in astronauts at the end of their mission; in Swedish volunteers who endured 77 hours of noise and sleep deprivation; and in people whose spouses had recently died. (All these studies showed decreases in the response of immune system cells to stimulation in the test tube.)

While the physical response to such extreme events is interesting, it's not immediately relevant to everyday life; fortunately, no one loses a spouse or goes for three days without sleep very often. But a decade ago, only a handful of PNI researchers had used human subjects—the vast majority of studies were still being done on rodents—and virtually all the human studies looked at the effects of extreme stress.

It was at that point that we began our research, which has been aimed at studying the connection between stress and immunity under more natural circumstances. Although we were married, we had never thought about working together. One of us (Janice Kiecolt-Glaser) was a psychologist whose research had focused on assertiveness training, while the other (Ronald Glaser) was an immunologist studying the possible role of Epstein-Barr virus in a form of nasal cancer. While our relationship was based on many things, the prospect of professional collaboration was not one of them.

But as we began to become aware of the growing body of research in PNI—which we each saw through the lens of our respective backgrounds—we realized that we had a unique opportunity to pool our disciplines and make a contribution together. In 1982, we began clinical studies at Ohio State University to try to synthesize the tantalizing but scattered findings on stress and immunity and to investigate their relevance to human health.

We reasoned that if stress was indeed an important risk factor for infectious disease (and perhaps for cancer as well), then immunological changes should be associated with ordinary stressful events as well as intense ones. To find out, we began conducting annual studies of medical students. Every year since 1982, we have collected immunological and psychological data from the students throughout the academic year, including the three-day period in which they take their examinations. We have found that the simple stress of exams adversely affects a very wide range of immunological functions.

For example, we found that exams brought about a decline in the activity of natural killer cells—the cells that fight tumors and viral infections. The body's production of an immune system chemical called gamma interferon, which stimulates the growth and activity of NK cells, decreased by as much as 90 percent during examinations. The medical students' T-cells also showed a poorer response to test-tube stimulation during examinations.
THE ANTIBODY RESPONSE: HOW IT WORKS

The diagram on the next page shows how the immune system mounts an antibody response against an invader, as well as the roles that various cells play in the process.

Billions of B-cells are on guard in the body at all times, each one geared to recognize a single specific kind of invader, or antigen. When an antigen appears in the bloodstream, it is “caught” by a receptor on the surface of the appropriate B-cell. Like the antibodies the B-cell will produce, this receptor has a molecular shape that fits only this specific antigen.

Next, the B-cell engulfs the antigen and exposes part of the antigen on its surface, where it can be recognized by a helper T-cell. When a helper T-cell recognizes the signal, it attaches itself to the B-cell and releases interleukins—chemicals that stimulate the B-cell to become an antibody factory called a plasma cell. The plasma cell then multiplies, and the cells it produces pump out millions of identical antibodies into the bloodstream, where they hunt down the invading antigen.

Antibodies can render invaders harmless in a number of ways. For example, they can latch onto toxic substances produced by bacteria, inactivating the toxins. The antibodies may coat the bacteria themselves, a process that attracts other immune system proteins or cells that then destroy the invader. Or they can latch onto a virus, making it impossible for that virus to infect the body’s cells.

In one of our recent medical-student studies, we placed catheters in students’ arms for 24 hours during a low-stress academic period, and then again during exams, so we could draw hourly blood samples to measure changes in stress hormones (which can affect immunological activity). Nurses waited outside the students’ classrooms during the day in order to get their hourly samples, and students slept in the university hospital’s research unit at night. William Malarkey, the endocrinologist who conducted the hormone studies, found that levels of adrenaline and noradrenaline increased significantly at exam time, during both waking and sleeping hours. These changes could have led to some of the immunological changes we have observed.

All these findings are especially meaningful when you consider that medical students are experienced at taking examinations; the simple fact that they have been admitted to medical school shows that they have repeatedly done
CELLULAR IMMUNITY: HOW IT WORKS
When an antigen such as a virus enters the bloodstream, it can trigger a cellular immune response in various ways. Any cell that has been infected by a virus can “present” the antigen to helper T-cells that are specially geared to recognize it. Specialized cells, called macrophages, also engulf invading antigens and present them to helper T-cells. Once the helper cells recognize the presence of an antigen, they mature and multiply rapidly, in order to enable the body to fight the invader. One way they do this is by helping to activate cytotoxic T-cells, which then find and destroy cells infected with the virus. (Helper T-cells also help carry out the antibody response.)

Well on college exams. Yet despite their relative competence in this stressful situation, it consistently regulates their immunological function to a lower level.

Are these studies relevant to those of us who no longer take exams? We think so. The stress of examinations should actually provide a good model for understanding people’s responses to other commonplace stressors—events that people experience on a fairly routine basis but that still cause stress. For example, the several days before you go on a vacation or a business trip are often filled with frenzied activities at work and at home. Your emotional response to the pressures of those periods may be quite similar to the medical students’ feelings of stress and anxiety as they cram for exams. Similarly, you may feel tension or strain if you have to spend several days in the company of your least favorite relatives. If the stress you experience in these common situations is similar to our medical students’ responses to academic pressures, your immune system, too, may show the effects.

By learning how to relax, however, you may be able to affect your immune system’s functioning. In one study, we took 34 medical students before exam time and randomly assigned half of them to a group where they were given hypnosis and relaxation training. During exams, we compared the immune function of students in the training group with that of the other students, who received no such training. We saw no difference at first: Students in the relaxation group showed the same average downward alterations in immune function as the others. But a closer look showed that the students trained in relaxation varied tremendously in how often they practiced their relaxation techniques. And those who took their relaxation seriously, who practiced the techniques often, showed significantly better immune function during exams than did those who practiced less frequently or not at all.

IS STRESS REALLY HARMFUL TO HEALTH?
Although the immunological changes we and others have measured are reasonably clear and consistent, they don’t necessarily demonstrate that everyday stress is a health hazard. In fact, no one really knows whether relatively small immunological changes can actually affect the incidence, severity, or duration of infectious disease or cancer. Equally little is known about the clinical value of psychological approaches that lead to small improvements in immune mea-
sures. The health effect probably depends on the type of approach, its intensity, the degree of immunological change, and prior health status.

Moreover, it is difficult to demonstrate clearly that stress has helped cause an infectious illness or that stress reduction has helped stave one off. Infections such as strep throat or the flu are relatively infrequent—most adults don't experience many such episodes each year—so changes in their frequency are extremely difficult to detect. This is a special problem because PNI studies can use only relatively small groups of human subjects, due to the time and expense of doing such studies.

Finally, any effort to find connections between emotions, immunity, and health will be complicated by the fact that people under stress are likely to have lifestyles that put them at greater risk of disease. They're more prone to alcohol and drug abuse, poor sleep habits, poor nutrition, and inactivity—all of which can affect immunity.

The 1991 New England Journal of Medicine study of stress and the common cold, mentioned above, is one of the most persuasive demonstrations that emotional factors can indeed have a measurable affect on health. In that study, psychologist Sheldon Cohen at Carnegie Mellon University and his colleagues inoculated volunteers with measured doses of a cold virus—five different viruses were tested—or a placebo, a noninfectious "dummy" shot. As expected, some of the volunteers came down with colds and some did not. But among the volunteers injected with any of the five viruses, the chance of getting a cold or respiratory infection was directly proportional to the amount of stress the volunteers said they had experienced during the past year. The study was the first well-controlled demonstration that stress can increase the risk of infection.

Those results notwithstanding, stress is only one factor in determining your risk of infectious disease. The frequency with which you are exposed to viruses or bacteria, of course, has a major effect. So does the overall status of your immune system. That's particularly important for older adults because the immune system declines with age.

Our best understanding at this point is that the people most likely to become ill in response to stress are probably those whose immune systems are already compromised to some extent, either by a disease like AIDS or by a natural process like aging. These people start out with poorer immunological defenses, so that small changes associated with stress could have more important consequences. But even young, generally healthy people may find themselves getting sick more often if they are subject to severe or ongoing, long-term stress.

WHEN STRESS BECOMES A CHRONIC PROBLEM

What happens when people are faced with a stressful situation that lasts months or years, such as caring for a family member with Alzheimer's disease? The weight of the evidence to date suggests that the immune system does not adapt to the situation, but stays active at a lower level.

Caring for a spouse or a parent with Alzheimer's disease or another progressive form of dementia is a major hardship. There is no treatment for Alzheimer's disease, the course of the illness is uncontrollable and unpredictable, and the only certainty is the patient's eventual death. Since survival time sometimes extends to more than 20 years after the onset of the disease, caregivers have described the process as a kind of living bereavement, in which they watch the personality and intellect of their loved one slowly disintegrate. For five years, we have been studying people who are caregivers for a loved one with Alzheimer's to see how the long-term stress affects their immunological responses.

Joe, a retired lawyer in his mid-sixties, is typical of the caregivers in our study. He began taking care of his wife full-time about five years ago. The first time we saw him, he told us how his wife's symptoms had worsened over the prior year. Joe and his wife used to spend time at their summer home, located on an island in the middle of a lake. When he helped his wife into the boat the previous summer, she became very upset and confused; and when they reached the island, she jumped out, yelling to bystanders that her husband was a thug who was attacking her.

Fortunately, the local people knew Joe and his wife, and they helped calm her down and bring her back to him. Now, however, he feels that he can no longer take her out in public because he is afraid that the same thing might happen again around strangers. But he also can't leave her home alone because she might injure herself accidentally or wander away. Joe's story is typical of many we hear. It's not surprising that caregivers for people with Alzheimer's disease have high rates of clinical depression, much higher than their counterparts in the general population.

In our study, published in 1991, we measured certain aspects of immune function in 69 people who were caregivers for a spouse with dementia and in
69 people from our community who were the same gender, roughly the same age, and had the same income level. (The caregivers had been providing care for an average of five years when we first saw them.) During the 13-month interval between the beginning of the study and the follow-up, caregivers showed decreases in three measures of cellular immunity, relative to the non-caregivers, and were ill for more days with respiratory tract infections. This study provides the first good evidence that chronic stress leads to chronically lower immune system activity—which in turn may lead to a higher rate of illness.

Although these findings are provocative, they don’t mean that everyone subjected to chronic stress will react in the same way. We found that the caregivers who were most distressed by their spouse’s erratic behavior were most likely to show large negative immunological changes. The same was true of caregivers who were dissatisfied with their close personal relationships at the start of the study. Conversely, other studies have shown that friends and family can help caregivers deal with this kind of stress; in one study of women whose husbands were being treated for urologic cancer, those who had higher levels of social support had better immune function than those who reported less support.

THE IMPORTANCE OF RELATIONSHIPS

Some of the strongest evidence in the area of PNI now shows that poor personal relationships and social support can adversely affect the immune system. Sociologist James House and his colleagues reviewed data from large, well-controlled epidemiological studies and concluded that stressful social relationships rivaled smoking, high blood pressure, high blood cholesterol, obesity, and physical inactivity as a risk factor for illness and early death (see Chapter 20). The immune system may be part of the connection that explains this link.

Studies of several diverse groups of research subjects have found that people who are lonely, as measured by psychological tests, tend to have poorer immune function. In one of our earlier studies, we found that the loneliest medical students had the lowest levels of NK cell activity. Similar links between loneliness and suppressed immunity have been found in groups of psychiatric patients and adolescents.

Looking at the flip side of loneliness, psychologist Sandra Levy and her colleagues at the University of Pittsburgh found a connection between supportive personal relationships and improved immune function in women with breast cancer. The researchers measured NK cell activity and gave the women psychological tests just after they had undergone their initial surgery to remove a tumor, and then again three months later, after they had begun radiation or chemotherapy treatments. Several psychological aspects of support were linked to higher NK cell activity, including support from their husbands or other intimate relationships, support from their physicians, and efforts by the patients to actively seek support as a way of coping with stress.

A good deal of our own research is now designed to measure the impact of relationships on the immune system. We have found, for example, that divorced people who have the most negative feelings about the separation or the most difficulty “letting go” of a former spouse tend to show the greatest downward regulation of the immune system (see Chapter 20).

Our studies also suggest that sharing your feelings about issues that trouble you can have a positive effect on immunity. In collaboration with psychologist James Pennebaker at Southern Methodist University, we studied students who agreed to keep journals in which they wrote their feelings about disturbing, traumatic events—an analogy for the process that takes place in the intimate relationship of psychotherapy. Students who went through this process, we found, had better immune system function and fewer visits to the university’s health clinic.

In our study with Pennebaker, 50 healthy undergraduates were asked to write either about personal and traumatic events or about trivial topics for 20 minutes a day during four consecutive days. The 25 students randomly assigned to the “trauma” writing group took the assignment seriously; the topics they discussed were personal and quite traumatic, ranging from problems with homesickness after coming to college, loneliness, and relationship conflicts, to parental problems such as divorce, family quarrels and family violence, and the death of a loved one. The “trivial” group had an assigned topic each day, such as descriptions of the shoes they were wearing or of a recent social event.

Although there were no immunological differences between the two groups before they began the writing assignment, differences emerged by the end of the study. Immune system cells from students who wrote about traumatic events showed greater activity in standard laboratory tests than did cells
HOW IMMUNE FUNCTION IS TESTED

Because it is difficult to measure the functioning of the immune system within the body itself, researchers have devised various laboratory methods to do so indirectly. Such studies are typically performed by taking a sample of white blood cells from the person being tested and exposing the cells to certain compounds, called mitogens, that essentially mimic an attack by a foreign substance. Healthy white blood cells will respond by secreting other compounds and by proliferating when stimulated by a mitogen. By comparing the activity of stimulated to unstimulated cells, and by tracking the mitogen response when a person is under varying degrees of stress, it is possible to see how stress affects this kind of immunological activity in that person.

There are many different kinds of immunological lab tests, but they can be roughly divided into two classes: qualitative and quantitative tests. The qualitative tests provide information about the relative activity levels of particular cells under particular conditions—a kind of "performance" measure. In contrast, quantitative tests show the actual numbers or percentages of different cell types relative to each other. In general, psychological stress appears to affect qualitative aspects of immunity—the activity of different cells—more than it affects quantitative aspects.

taken from the blood of the other students, suggesting improved immune responsiveness.

With the students' permission, we then looked at their health center records. We compared the average rate of visits for illness during the five months prior to the study with the rate over a six-week period beginning at the time of the study. Students who wrote about traumatic events showed a drop in clinic visits, relative to those who wrote about trivial events.

STRESS AND SPECIFIC CONDITIONS

In addition to studying immune system changes in experiments like these, a number of researchers (including ourselves) have looked at conditions and diseases that involve the immune system to see if psychological factors might alter their course.

HERPES VIRUSES

Several recent studies have provided strong evidence that stress increases both the initial risk of developing a herpes infection and the risk that symptoms will recur.

Unlike other common viruses, which are usually eliminated from the body by the immune system, herpes remains in the body for life and may flare up unpredictably. Different kinds of herpes viruses cause genital herpes, cold sores, mononucleosis, cytomegalovirus infection, and chicken pox and shingles.

Several studies have now shown that stress can disrupt the body's immune response to these viruses. One study followed West Point cadets for the four years after they entered the military academy. Those cadets who had three risk factors for stress—a high level of motivation for a military career, poor academic performance, and fathers who were "overachievers"—were more likely to develop infectious mononucleosis and were hospitalized longer in the infirmary. (None of the cadets in this study were infected with Epstein-Barr virus, the cause of mononucleosis, when they entered the academy.) Other studies have shown that nursing students who tend to be unhappy (as measured by psychological testing) are more likely to have recurrent cold sores, and that unhappy people in general have higher rates of recurrent genital herpes.

Some studies have used blood samples to measure the body's response to herpes viruses under stress. The cellular arm of the immune system is responsible for controlling both the initial herpes virus infection and later recurrences. When cellular immunity fails to do its job, the body may try to fight off the virus by producing antibodies to it. Paradoxically, then, high blood levels of antibodies to herpes viruses mean the immune system is not controlling the virus effectively; in other words, high antibodies to herpes are a sign of low immune function. For example, medical students have higher levels of antibodies to certain herpes viruses during final examinations and lower levels after summer vacation.

People under various kinds of stress tend to have high levels of antibodies to herpes viruses, even if they don't develop symptoms of infection. In the West Point study, for example, even cadets who did not get sick were more likely to have high antibodies to Epstein-Barr virus (EBV) if they were in the
high-stress group. In another study, separated and divorced men and women had higher EBV antibody levels than a group of married volunteers of the same age and education. (The separated and divorced men also had high levels of antibodies to HSV-1, the herpes virus that causes cold sores.) Caregivers for family members with Alzheimer’s disease have higher EBV antibodies than similar people in the community, and psychiatric inpatients have higher HSV-1 antibody levels than people with no psychiatric disorders. Taken together, all these studies provide consistent and convincing evidence that stress can affect the body’s control over herpes virus infections.

ALLERGIES

Allergies are triggered when the immune system becomes oversensitized to something in the environment—such as pollen grains or a particular food—and overreacts with an intense inflammatory response whenever the allergen is present. In the case of hay fever, for example, exposure to pollen grains sets off the production of massive amounts of antibodies, which in turn signals a class of white blood cells, called mast cells, to spring into action. The mast cells then produce a chemical called histamine, which in turn inflames the nasal passages and causes sneezing, itching, and tearing eyes.

While it is not clear whether stress can trigger or worsen allergies, there is good evidence that the mind can affect the allergic response in other ways. Animal experiments have shown that allergies can be learned as a conditioned response. In one study, guinea pigs were sensitized to a specific chemical—in essence, made allergic to it—and then repeatedly exposed to that chemical at the same time that they were made to smell an innocuous, unrelated odor. After a few weeks, the odor alone would trigger the release of histamine in these animals, just as if they had been exposed to the allergen.

A few studies have suggested, too, that people can modulate the allergic response under hypnosis. Some of the better studies have used the “double-arm” technique: Both arms are injected with substances that produce an allergic response, but the subject is told under hypnosis that only one arm will show the redness, itching, burning, and swelling that characterize an allergy. In most of these experiments, though not all, one arm is indeed more affected than the other. However, the difference may be due simply to circulatory changes in the skin rather than to a difference in the underlying immune response.

AUTOIMMUNE DISEASE

Autoimmune diseases, like allergies, stem from excessive immune system activity. In these diseases—which include rheumatoid arthritis, systemic lupus erythematosus, and Type I diabetes—the immune system becomes overactive or imprecise in its duties. Antibodies or immune system cells mistakenly identify the body’s healthy cells as foreign invaders and attack them. The results are chronic inflammation and, in some cases, life-threatening organ damage.

The possibility that stress is linked to autoimmune disease is intriguing but still speculative. It is not immediately clear how stress could precipitate these illnesses; chronic stress is typically associated with immune suppression, although acute stress can activate the immune system. But a number of anecdotal reports suggest that there could be a link—perhaps operating through an immunological pathway that has not yet been discovered—and several researchers are beginning to study that possibility.

CANCER AND AIDS

These two diseases, perhaps the most feared of all modern illnesses, are generally modulated by the immune system. According to one widely held theory, cancer cells arise in the body all the time, but they are normally held in check by immune cells that recognize them as invaders and destroy them: it is only when these cells are ineffective that cancer spreads. And AIDS, the ultimate immunological disaster, results from the wholesale destruction of the cellular immune system, caused by a virus that invades and kills key “helper” T-cells.

One area of great interest is the possibility of using mind/body techniques to influence cancer and AIDS by improving the immune response. Although a number of clinicians have advocated the use of such techniques as guided imagery for cancer patients, there is no good evidence that this has a direct physiological benefit for people with cancer. However, a few recent studies—described in detail in Chapters 5 and 20—now suggest that group therapy, oriented toward relaxation training and psychological support, may improve certain components of the immune response and possibly survival for people with certain kinds of cancer. Similarly, early studies show that stress management groups and exercise can help maintain immune function in men infected with HIV, the virus that causes AIDS (see Chapters 19 and 23).
THE EVIDENCE FOR PNI—AN OVERVIEW

Robert Ader, a psychologist at the University of Rochester School of Medicine and Dentistry, performed the key experiments in the mid-1970s that ushered in the field of psychoneuroimmunology (PNI). Today, he is coeditor of the major reference work in the field, Psychoneuroimmunology, and editor-in-chief of its primary journal, Brain, Behavior, and Immunity, as well as an active researcher. In a recent interview with the editors of this book, he summarized the essential evidence that has been found to date for connections between the mind, the immune system, and the nervous system, as follows:

Nerve endings have been found in the tissues of the immune system.
The central nervous system is linked both to the bone marrow and thymus, where immune system cells are produced and developed, and to the spleen and lymph nodes, where those cells are stored.

Changes in the central nervous system (the brain and spinal cord) alter immune responses, and triggering an immune response alters central nervous system activity. Animal experiments dating back to the 1960s show that damage to different parts of the brain's hypothalamus can either suppress or enhance the allergic-type response. More recently, researchers have found that inducing an immune response causes nerve cells in the hypothalamus to become more active and that this brain cell activity peaks at precisely the same time that levels of antibodies are at their highest. Apparently, the brain monitors immunological changes closely.

Changes in hormone and neurotransmitter levels alter immune responses, and vice versa. As this chapter and the previous one have shown, the "stress hormones" generally suppress immune responses. But other hormones, such as growth hormone, also seem to affect immunity. Conversely, when experimental animals are immunized, they show changes in various hormone levels.

Lymphocytes are chemically responsive to hormones and neurotransmitters. Immune system cells have receptors—molecular structures on the surface of their cells—that are responsive to endorphins, stress hormones, and a very wide range of other hormones as well.

Lymphocytes can produce hormones and neurotransmitters. When an animal is infected with a virus, lymphocytes produce minuscule amounts of many of the same substances produced by the pituitary gland.

Activated lymphocytes—cells actively involved in an immune response—produce substances that can be perceived by the central nervous system. The interleukins and interferons—chemicals that immune system cells use to "talk" to each other—can also trigger receptors on cells in the brain, more evidence that the immune system and the nervous system speak the same chemical language.

Psychosocial factors may alter the susceptibility to, or the progression of, autoimmune disease, infectious disease, and cancer. Evidence for these connections comes from many researchers (and is cited in this chapter and others in this book).

Immunologic reactivity may be influenced by "stress." Chronic or intense stress, in particular, generally makes immune system cells less responsive to a challenge.

Immunologic reactivity can be influenced by hypnosis. In a typical study of this type, both of a subject's arms are exposed to a chemical that normally causes an allergic reaction. But the subject is told, under hypnosis, that only one arm will show the response—and that, in fact, is often what happens.

Immunologic reactivity can be modified by classical conditioning. As Ader's own key experiments showed, the immune system can "learn" to react in certain ways as a conditioned response.

Psychoactive drugs and drugs of abuse influence immune function. A range of drugs that affect the nervous system—including alcohol, marijuana, cocaine, heroin, and nicotine—have all been shown to affect the immune response, generally suppressing it. Some psychiatric drugs, such as lithium (prescribed for manic depression), also modulate the immune system.
VACCINATION
Vaccines help protect us from disease by providing the immune system with a "sneak preview" of a disease-causing bacterium or virus, thus priming the system for a quick attack if that organism later makes a real assault on the body. Because stress can clearly affect immune function, might it also affect the response to a vaccine?

A recent study from our laboratory shows that it can. We gave each of three vaccinations against hepatitis B to 48 medical students on the last day of a stressful examination period. As expected, a few students made antibodies to the hepatitis virus after the first injection—the sign of a stronger immune response. Others made antibodies only after a booster shot, and some required all three shots before responding. Our research showed that the small number of students who produced antibodies after the first injection—25 percent of the total group—were less stressed and less anxious than those who required two or three shots to trigger antibody production. These data suggest that the response to a vaccine can be affected by a relatively mild stressor in young, healthy adults—a finding that may have important public-health implications.

THE BOTTOM LINE
Taken together, the evidence from human and animal studies clearly shows that stress can suppress immune function. For most stressors, these immune system changes may be quite small and probably will not have any severe consequences, particularly if you are otherwise healthy. But if you have recently experienced a major disruption in your life, like a divorce or a move, then your health may indeed be affected, especially if age or a medical condition has already weakened your immune system.

Relaxation, group support, and other forms of stress management may well enhance immunity. One caveat, however: If your immune system is already functioning well, it may not be possible to "enhance" it above normal levels.

The evidence suggests that there are things you can do to improve your chances of staying healthy—beyond following such basic preventive advice as getting flu shots, eating sensibly, exercising, and getting enough sleep. If you feel you are under serious stress, you may want to try one of the many stress reduction programs now available. In addition, it may be helpful to talk about your feelings with people close to you or with a therapist; supportive personal relationships appear to help maintain the immune response and physical health.

What if you have a serious illness like cancer or are infected with the AIDS virus? First and foremost, continue with standard medical treatments recommended by your physician. No form of relaxation, support, or imagery can substitute for the well-documented benefits of standard medical care, though they may complement it. As an adjunct to your medical treatment, you may want to consider joining a group for people who have cancer or who are HIV-positive or meet with a mental health professional accustomed to dealing with medically ill patients.

Finally, whatever you do, don't blame yourself for any negative changes in your health. Although the results of PNI research are promising and are beginning to suggest ways that we can affect the balance between health and disease, remember that we still know little about the extent to which these approaches can actually be used to improve health. Rather than leading you to blame yourself for your illness, this research should motivate you to do whatever possible to stay healthy.