Stress and the Immune System

Some people believe that their cancer was caused by stress, or that it will be made worse by stress, or that perhaps they have a cancer-prone personality. Many research studies have attempted to discover links between cancer, stress, depression, personality, and coping skills. The connections are complex.

First, there is no consistent evidence that stress causes or worsens cancer. Studies done using animals and humans do not consistently show a positive association between stress and cancer, not even when underlying disease already exists. In fact, in some animals, some forms of stress cause tumors to shrink.

Second, the few studies that hint at a link between personality and cancer are not conclusive for various reasons, such as the design of the study.

This fact sheet describes the known associations—or the lack of them—between stress, the immune system, illness, and cancer.

What is stress?

Experts in various fields of medicine and psychology recognize many different circumstances and events as stressful. Depending on the circumstances or point of view, stress could be viewed as a threatening object or the event itself, the physical reaction within our bodies to the threat, or the state of mind that precedes our taking some action in response to threat.

To the psychiatrist studying brain chemistry, our awakening in the morning and the corresponding rise or fall in levels of several hormones may be viewed as a stressful event for the constantly adapting brain. For the psychologist, overcrowding of humans in urban areas can be viewed as a stressful event. For an orthopedic surgeon, the impact sustained by cartilage within the knee when one runs on concrete is viewed as stress.

The psychoneuroimmunologist, however, views the interaction of the immune system with the central nervous system as an adaptation to stress. This interpretation, which can accommodate both physical and emotional stress, will be the chief focus of this article.

Responses to stress

Our bodies and minds respond to stress in many ways. These adaptations may change with the type and intensity of the stressor, the amount of time we have been exposed to it, our previous experiences trying to adapt to similar stressful events, the person experiencing stress, and his or her physical and emotional state at the time.

Although many emotional responses to stress are possible, such as anger and withdrawal, the responses most often reported by cancer survivors are fear, anxiety, and depression. The National Cancer Institute reports that during and after diagnosis and treatment, almost half of all cancer patients report anxiety and about a quarter report significant anxiety. Twenty percent experience transient or long-term depression, and 15 percent are diagnosed with post-traumatic stress disorder. Estimates by other researchers are sometimes much higher.

Fear is sometimes useful

Several bodily changes occur as a reaction to a fearful event. During fear, hormones that prepare us to adapt to stress are released in a chain reaction, first from the brain, which trigger in turn the release of stress hormones from the adrenal glands. Our heart rate increases, blood is redirected to body parts associated with fight or flight, and extra sugar is made available in the bloodstream via the liver.

Fear can be a useful, goal-oriented reaction to a stressor. Each of these physical changes is aimed either at our fleeing from danger or conquering it bodily.

Fascinating research into brain structure and function has shown that the amygdala, part of the “old brain” conserved in most creatures from reptiles up through the primates, including humans, is the brain organ responsible for finding safety quickly when fear arises. Direct connections between the amygdala and our sensory organs bypass the higher brain centers of decision-making, allowing us to react very quickly to threats, sometimes without our being aware that we have perceived them. For instance, if you hike in the woods, have you ever stopped abruptly after sensing just a muted change

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of color or pattern, and upon closer inspection realize that subtle difference is a snake? This brain connection is probably responsible for the immediate, calm, highly effective, goal-oriented behavior that some people exhibit in unbelievably horrifying situations.

Although fear doesn't feel good, it can be a useful, goal-oriented reaction to a stressor. It galvanizes us and prepares us for action. The extreme and immediate physical reaction to fear, however, does little or nothing to prepare us to deal intellectually with a fearful situation that requires extensive analysis, planning, and decision-making, such as absorbing the technical medical information about our cancer diagnosis. On the contrary, research has shown that both very low and very high levels of the stress hormones from the adrenal gland interfere with learning new tasks. Short of our ability to jump up and flee the doctor's office or our sudden acquisition of strength to throttle the bearer of bad news, we have been poorly prepared by evolution for dealing with cancer as a stressful event. As a result, an out-of-phase mismatch of events is what many of us experience when being told of the cancer diagnosis—with a strong likelihood that we will remember forever and with great acuity the perceptual cues that were present, instead of the key points that the doctor attempted to relay.

Anxiety is unhealthy

Most adults have experienced the difference between fear and anxiety. Fear is an acute, strong, visceral response to stress. Anxiety is a nagging, chronic, or generalized fear response. Although some would choose the chronic physical distress of anxiety over the pronounced physical distress of fear, anxiety may be the more physically harmful of the two experiences.

Unresolved fear may convert to anxiety as we begin to grow accustomed to a threat. When we're anxious, the same physical changes that accompany fear occur at lower levels, with deleterious effects on our body. Sustained increased heart output and constriction of blood vessels to rechannel blood to certain organs can contribute to the development of high blood pressure and cardiovascular disease. Altered sugar metabolism can worsen diabetes. The tendency for digestive activity to increase in times of stress can exacerbate underlying gastrointestinal disease.

Worry and anxiety involve recycling the same fear, repeatedly examining the outcomes and evaluating interventions. We sometimes use this activity to justify worry, assuming that repeated scrutiny will result in knowing what to do if worse comes to worst, but this continual rehearsal of negative events in search of solutions may not benefit us should danger actually arise. The two thought processes, worry and planning, center in different parts of the brain. On magnetic resonance imaging, those who worry show activity in the emotional part of the brain, whereas those who plan show activity in the opposite hemisphere, the so-called logical half of the brain. This may mean that, from the standpoint of providing a good solution in the face of danger, worry is not the best strategy. Worry does not determine the best solution and move on to the next problem. It prevents us from detecting and dealing with new problems in a timely and effective way.

Physical symptoms of anxiety may include any of these: shortness of breath, sigh breathing, dry mouth, inability to swallow, trembling, weakness, incessant crying, circular or obsessive thoughts, inability to concentrate, paralytic or manic movements, insomnia, headache, recurrent nightmares, or extreme fatigue.

What feels like anxiety is not always caused by worry. Sometimes it can have physical causes. In some cases, symptoms that are indistinguishable from anxiety can be caused by the tumor itself:

- Non-Hodgkin's lymphoma tumors in the lung can cause shortness of breath.
- Tumors in parts of the kidney can stimulate the adrenal gland to overproduce cortisol, a hormone released during fearful episodes.
- Tumors of the brain near or in the pituitary can stimulate hormones that in turn stimulate the adrenals to overproduce cortisol.

These medications taken as anticancer therapy also can cause anxiety:

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- Corticosteroids such as prednisone.
- Bronchodilators and certain other drugs used for asthma.
- The newer antidepressant drugs to control nausea and pain, such as Prozac.
- Cessation of the use of the quick-acting anti-anxiety drugs, such as Valium or Ativan.

Certain physical changes that accompany incipient medical conditions are heralded by feelings of anxiety:

- Pneumonia
- Heart attack
- Electrolyte imbalance
- Angina

But the chief cause of anxiety among cancer survivors is worry and sustained, unresolved fear. Fear of pain, of abandonment, of dependency, of financial ruin, of professional ruin, of relapse, of death.

When we worry for a long time about one problem, new electrical circuitry is laid in our brains. Sometimes conditions resembling or related to our problem will trigger anxiety symptoms or symptoms of physical distress. Many cancer survivors report anticipatory nausea just smelling the rubbing alcohol used to clean the skin over a vein before chemotherapy is administered. Studies have shown that this response can cause their blood counts to drop—even if they are not given chemotherapy in that session.

Obviously this reaction, called a conditioned response, can have a direct impact on the immune system, as has been demonstrated many times in animals. For example, when rats in one experiment were fed a combination of immune suppressant and saccharine dissolved in water, their white blood cell counts dropped afterward, as expected. When the experiment was repeated using only saccharine in water, white blood cell counts still dropped. This demonstrates that the association of event and outcome does not require knowing, for example, what chemotherapy is intended to do. Physiological cause and effect can occur in the absence of the cognitive processes as we know them today.

This does not imply, of course, that you can skip chemotherapy because just thinking about it may have some of the same effects. There's no evidence that a conditioned drop in blood counts coincides with an attack by the immune system on tumor cells.

Beth, the daughter of a man with non-Hodgkin's lymphoma, describes how long-term anxiety has taken its toll on her:

> *I need to try something to reduce stress. I don't think I really deal with things head-on, and I end up transferring the stress to my body. I've just had horrible chest pains and insomnia lately, and my stress level is becoming horrendous. I've never been that great at dealing with it. I'm not even the one who has lymphoma, but it seems all I can do is worry, worry. I've tried meditation, but I can't keep up with it. I even work out at least weekly, and I have a pet. I don't know what to do next.*

Depression

Research has shown that those who are depressed often have suboptimal immune system function.

Most cases of depression that coincide with cancer are called situational depressive episodes, directly related to the stress of adjusting to cancer. These depressive episodes differ from organic disturbances such as manic depression or unipolar depression, unless the person has had episodes of these diseases in the past, well before the cancer diagnosis.

Depression may be diagnosed if one or more of the following symptoms persist for more than two weeks:

- Despair
- Excessive sleepiness
- Insomnia
- Appetite disturbance
- Irritability
- Inability to function

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- Loss of interest in sex and other pleasurable activities
- Thoughts of suicide

Cancer-related problems that seem to have no solution can cause depression. When we experience repeatedly that our efforts to solve problems don't work or are punished, we cease trying. This is called learned helplessness by experts, but we know it as despair, and it is linked to depression. Subsequently, when new problems arise that we could indeed solve, or when new methods of dealing with old problems emerge, those exhibiting learned helplessness fail to act. A therapist trained to deal with depression can help overcome learned helplessness and despair.

In addition to the psychological factors surrounding cancer that can cause depression, so might the following:

- Chemical treatments for cancer that are neurotoxic or toxic to the thyroid, such as Taxol, prednisone, interferon alfa, or interleukin-2 can cause chemically induced depression.
- Hemorrhagic stroke that may result from untreated symptoms of some NHLs can cause depression after blood products that cannot be cleared settle in the brain.
- High doses of cranial irradiation for NHL therapy that are not accompanied by steroid therapy may cause depression. Depression is but one of a constellation of symptoms following cranial irradiation.

Please note that the preceding three points are possible side effects that do not necessarily occur in every person.

The effect of stress on the immune system

The stress hormones released by the adrenals during episodes of fear and anxiety also affect white blood cells, the infection-fighting army within our blood. Initially, the surge of brain and adrenal hormones that accompanies stress causes an increase in circulating white blood cells. When cortisol remains high, however, white blood cell numbers are reduced. As stress, anxiety, or depression continue unabated over weeks or months, output of the adrenal hormone cortisol is consistently high and white blood cell numbers remain reduced.

Stress and cancer

If prolonged stress and resulting anxiety affect the number of white blood cells in our body, does this mean that cancer can be caused by or made worse by stress? The answer, based on animal and human research, is unclear.

Animal studies support what many recognize intuitively: if stress had an unequivocal link to the development of cancer, just about every one of us would develop cancer. If stressful life events within the last three years were responsible for the emergence of cancer, then everyone who survived imprisonment in Auschwitz and other Nazi annihilation camps ought to have been diagnosed with cancer soon after being freed by the Allies. Continuing with the same analogy, all people who are diagnosed with cancer should either develop a second cancer triggered by the stress of the first diagnosis or should never be able to recover from the first cancer. Likewise, all loved ones of those diagnosed with cancer should then develop a cancer from dealing with the stress of their loved ones' suffering.

In fact, animal studies show a very wide range of tumor response to stress, depending on the type of stressor used, the ability of the animal to modify or escape the stressor, the species being tested, the gender, the animal's previous experience with this stress, whether the tumor was chemically induced or transplanted, whether the tumor is primary or a metastasis, and so on. In some cases, stress causes animal tumors to shrink.

Human studies have been to date somewhat less direct in measuring stress and tumor response, because few humans would tolerate having tumors chemically induced or transplanted, or being deliberately subjected to stress. The best study design would follow cancer-free people for years, recording stressful events and subsequent cancer diagnoses.

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Most human studies so far have relied on retrospective self-reports of stress levels prior to the cancer diagnosis. This method of collecting information is often criticized as of dubious reliability. For instance, a person who has just been diagnosed with cancer and who has agreed to fill out a questionnaire on life factors may report that other recent stressful life events were not very stressful. Compared to this newest problem, cancer, indeed these events may in retrospect seem not to be. Yet at the time the previous stressful events occurred, they may have been perceived and reacted to as very stressful events.

In short, while stress has been undeniably linked, over and over, to increased rates of some illness such as upper respiratory infection and certain autoimmune disease, there is no clear causative link between stress and cancer.

Is there a cancer personality?

If stress causes both emotional and physical changes but does not consistently have a part in the development of cancer, what other factors might be responsible? Can the ways a person adapts to stress affect his or her health? Do habitual ways of adapting hint at a "cancer personality"? The evidence, based on animal and human research, is conflicting.

Obviously, animal studies on this topic are difficult to perform because we can't know with certainty what animals are feeling, so most studies are done on humans. Often the design of these studies has been criticized.

For instance, melancholia, or what we would call depression today, received attention in the past as a personality trait possibly linked to cancer, but we know today that depression is less a personality trait or coping mechanism than an imbalance in brain chemistry with many different causes including genetics, situational adjustment, influenza, and stroke.

One study of breast cancer survivors assessed personality and coping styles, using a questionnaire and interview the day before breast biopsy. They concluded that women who were stoical and "psychologically morbid" rather than expressive and emotional were more likely to have malignant findings in biopsied tissue. Here are some reasons why the designs of studies of this kind are criticized:

- Those of us who have had biopsies know that this is often a stressful experience, likely to derail our responses, if we are able at all to take such an interview seriously in this very emotionally charged setting.
- Suppose those found to have a malignancy already had a good idea what their diagnosis might be? Suppose this idea had time to develop for a week or two while they waited for the surgery? Would the women questioned be likely to display more evolved, thought-out, stoical coping styles, perhaps not consistent with their usual more spontaneous reactions? In fact, some of the women in this study indeed had been informed by their radiologists that the lesions appearing on mammography were most likely malignant.
- How can we know that the answers on a questionnaire, even when the anxiety surrounding a biopsy is not an issue, reflect how someone really behaves?
- Suppose coping styles early in life predispose us to breast cancer, but our coping styles at maturity are what is measured by these questionnaires?
- What kind of person volunteers to fill out a questionnaire? (Questionnaire studies always face this criticism.) Would emotional women be more likely to decline, and stoical women more likely to comply? Or if a small honorarium is offered, say about thirty dollars, as is common for many psychological studies, will less affluent women be over-represented because for affluent women the invasion of privacy and the time lost isn't worth thirty dollars? If so, do less affluent women have other life conditions that would predispose them to breast cancer, such as living in an air-polluted neighborhood?
- Suppose the behavior described as stoical is an artifact of some other circumstance, such as working long, exhausting hours under artificial

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light for several years? Other, equally plausible theories suggest that the increasing rate of breast cancer is linked to increasing lifetime estrogen exposure. Studies have demonstrated that estrogen exposure begins earlier now, for the age of first menstruation has steadily decreased in industrialized countries since the use of electric light became widespread in the twentieth century.

- And finally, if this study had been designed in an era when being stoical was admired and being expressive was considered "psychologically morbid," would the researchers have attempted to prove that expressive women were more likely to develop breast cancer?

The supposed link between personality and the development of cancer is a tenuous one.

What can we do?

If fear is not very useful in dealing with cancer, and anxiety and depression pose risks for long-term health problems, what reactions and responses deal effectively with cancer-related stress? And if stress is not linked conclusively to the inception or growth of tumors and may in fact shrink tumors in some cases, why attempt to reduce the stress that is associated with the cancer experience?

First, most people prefer feeling good to feeling bad. Stress reduction techniques can help you feel better.

Second, increased levels of stress clearly are tied to the worsening of certain illnesses, such as upper respiratory infections. If you've decided on a course of chemotherapy or radiation therapy, your immune system may be compromised for a few days or a week during each cycle. It's best to avoid infections and to minimize those that may arise during these troughs. Stress reduction techniques may help you keep secondary health problems at a minimum while undergoing anticancer therapy.

Third, high levels of stress for long periods of time can contribute to the development of high blood pressure, gastric disease, migraine headaches, certain autoimmune diseases, and other stress-related illnesses.

This fact sheet was adapted from *Non-Hodgkin's Lymphomas: Making Sense of Diagnosis, Treatment, and Options,* by Lorraine Johnston, For more information, call **(800) 998-9938** or see *www.patientcenters.com.*