The Heavy Cost of Chronic Stress

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In this season of bickering relatives and whining children, of overcrowded department stores and unwritten Christmas cards, it is instructive to consider the plight of the Pacific salmon.

As the fish leap, flop and struggle upstream to spawn, their levels of cortisol, a potent stress hormone, surge, providing energy to fight the current. But the hormone also leads the salmon to stop eating. Their digestive tracts wither away. Their immune systems break down. And after laying their eggs, they die of exhaustion and infection, their bodies worn out by the journey.

Salmon cannot help being stressed out. They are programmed to die, their systems propelled into overdrive by evolutionary design.

Humans, on the other hand, are usually subject to stresses of their own making, the chronic, primarily psychological, pressures of modern life. Yet they also suffer consequences when the body's biological mechanisms for handling stress go awry.

Prolonged or severe stress has been shown to weaken the immune system, strain the heart, damage memory cells in the brain and deposit fat at the waist rather than the hips and buttocks (a risk factor for heart disease, cancer and other illnesses), said Dr. Bruce S. McEwen, director of the neuroendocrinology laboratory at the Rockefeller University and the author of a new book, "The End of Stress as We Know It." Stress has been implicated in aging, depression, heart disease, rheumatoid arthritis and diabetes, among other illnesses.

Researchers have known for many decades that physical stress takes a toll on the body. But only relatively recently have the profound effects of psychological stress on health been widely acknowledged. Two decades ago, many basic scientists scoffed at the notion that mental state could affect illness. The link between mind and body was considered murky territory, best left to psychiatrists.

But in the last decade, researchers have convincingly demonstrated that psychological stress can increase vulnerability to disease and have begun to understand how that might occur.

"If you would have said to me back in 1982 that stress could modulate how the immune system worked, I would have said, `Forget about it,' " said Dr. Ronald Glaser, an immunologist at Ohio State University.

The more researchers have learned, the clearer it has become that stress may be a thread tying together many illnesses that were previously thought to be unrelated.

"What used to be thought of as pathways that led pretty explicitly to one particular disease outcome can now be seen as leading to a whole lot of different outcomes," said Dr. Robert M. Sapolsky, a professor of neurology at Stanford.

Central to this new understanding is a novel conception of stress, developed by Dr. McEwen, who has been studying the subject for more than three decades. According to his model, it is not stress per se that is harmful. Rather, the problems associated with stress result from a complicated interaction between the demands of the outside world and the body's capacity to manage potential threats.

That capacity can be influenced by heredity and childhood experience; by diet, exercise and sleep patterns; by the presence or absence of close personal relationships; by income level and social status; and by the piling on of normal stresses to the point that they overload the system.

In moderate amounts, the scientists argue, stress can be benign, even beneficial, and most people are equipped to deal with it.

Preparing to give a speech, take a test or avoid a speeding car, the body undergoes an elaborate series of adjustments. Physiological processes essential in mobilizing a response - the cardiovascular system, the immune system, the endocrine glands and brain regions involved in emotion and memory - are recruited into action. Nonessential functions like reproduction and digestion are put off till later.

Adrenaline, and later cortisol, both stress hormones secreted by the adrenal glands, flood the body. Heart rate and blood pressure rise, respiration quickens, oxygen flows to the muscles, and immune cells prepare to rush to the site of an injury.

When the speech is delivered, the test taken or the car avoided, another complex set of adjustments calms things down, returning the body to normal.

This process of "equilibrium through change" is called allostasis, and it is essential for survival. But it was developed, Dr. McEwen and Dr. Sapolsky point out, for the dangers humans might have encountered in a typical day on the savannah, the sudden appearance of a lion, for example, or a temporary shortage of antelope meat.

Blaring car alarms, controlling bosses, two-career marriages, six-mile traffic jams and rude salesclerks were simply not part of the plan.

When stress persists for too long or becomes too severe, Dr. McEwen said, the normally protective mechanisms become overburdened, a condition that he refers to as allostatic load. The finely tuned feedback system is disrupted, and over time it runs amok, causing damage.

Work that Dr. McEwen and his colleagues have conducted with rats nicely illustrates this wear-and-tear effect. In the studies, the rats were placed in a small compartment, their movement restricted for six hours a day during their normal resting time. The first time the rats were restrained, Dr. McEwen said, their cortisol levels rose as their stress response moved into full gear. But after that, their cortisol production switched off earlier each day as they became accustomed to the restraint.

That might have been the end of the story. But the researchers also found that at 21 days, the rats began to show the effects of chronic stress. They grew anxious and aggressive. Their immune systems became slower to fight off invaders. Nerve cells in the hippocampus, a brain region involved in memory, atrophied. The production of new hippocampal neurons stopped.

Dr. Sheldon Cohen, a professor of psychology at Carnegie Mellon University, has found that people respond much the same way. Among volunteers inoculated with a cold virus, those who reported life stresses that continued for more than one month like unemployment or family problems were more likely to develop colds than those who reported stress lasting less than a month. The longer the stress persisted, the greater the risk of illness.

Allostatic load is often made worse, Dr. McEwen said, by how people respond to stress, eating fatty foods, staying late at work, avoiding the treadmill or drinking to excess. "The fact is that we're now living in a world where our systems are not allowed a chance to rest, to go back to base line," he said. "They're being driven by excess calories, by inadequate sleep, by lack of exercise, by smoking, by isolation or frenzied competition."

The Chemistry: Shrinking Cells, Turned-Off Responses

Doctors sometimes dismiss stress-related complaints as "all in the patient's head." In a sense, they are right. The brain, specifically the amygdala, detects the first signs of danger, as demonstrated in now-classic studies by Dr. Joseph LeDoux of New York University. Other brain areas evaluate the threat's importance, decide how to respond and remember when and where the danger occurred, increasing the chances of avoiding it next time.

So it is not surprising that when the stress system is derailed, the brain is a target for damage. A decade of research has demonstrated that sustained stress and the resulting overproduction of cortisol can have chilling effects on the hippocampus, a horseshoe-shaped brain structure intimately involved in memory formation.

Scientists say they believe that the hippocampus plays an active role in registering not only events, but also their context, an important task in the face of danger. In stressful situations, the hippocampus also helps turn off the stress response after the threat has subsided.

But high levels of cortisol, studies have shown, can shrink nerve cells in the hippocampus and halt the creation of new hippocampal neurons. These changes are associated with aging and memory problems. Some evidence also links a smaller hippocampus with post-traumatic stress disorder, depression and sexual abuse in childhood, though the meaning of this size difference is still being debated.

Like other hormones, cortisol normally rises and falls with daily rhythms, its production higher in the morning and lower in the evening. Prolonged or severe stress appears to disrupt the cycle. Chronically stressed people sometimes have higher base line cortisol levels and produce too much or too little of it at the wrong times.

One result, recent studies indicate, is that fat is deposited at the abdomen rather than the hips or the

buttocks. One of cortisol's primary functions is to help mobilize energy in times of acute stress by releasing glucose into the blood. But when cortisol remains chronically elevated, it acts, along with high insulin levels, to send fat into storage at the waist. This makes sense if a famine looms. But it is bad news for anyone who wants to minimize the risk of heart disease, cancer and other illnesses.

Studies have shown that excess cortisol secretion in animals increases visceral fat. And Dr. Elissa S. Epel at the University of California at San Francisco has found that even in slender women, stress, cortisol and belly fat seem to go together.

The notion that being stressed makes people sick is a popular one, and most people subscribe to some version of it. Come down with the flu in the midst of a messy divorce or a frantic period at the office, and someone is bound to blame stress.

But it was not until the 1980's and early 90's that scientists began to discover the mechanisms that might lie behind the mind and body link. Investigators uncovered nerves that connect the brain with the spleen and thymus, organs important in immune responses, and they established that nerve cells could affect the activity of infection-fighting white blood cells.

Scientists also found that cytokines, proteins produced by immune cells, could influence brain processes. Among other things, the proteins appeared able to activate the second major phase of the stress response, the so-called hypothalamic-pituitary-adrenal, or H.P.A., axis. In this chemical sequence, the hypothalamus, situated in the forebrain, dispatches chemical signals to the pituitary, which in turn secretes the stress hormone ACTH, prompting the adrenal glands to produce cortisol.

Much remains unknown about how the brain, the endocrine system and the immune system interact, and some of what is known is not well understood. For example, high levels of cortisol have long been known to shut off the production and action of cytokines, which initiate the immune response. At normal levels, cortisol can enhance immunity by increasing the production of inflammation-fighting cytokines. Yet in some cases, it seems, cortisol does not properly shut down the immune system under stress, allowing the continued production of cytokines that promote inflammation. These cytokines have been linked to heart disease, depression, stroke and other illnesses.

Still, scientists can watch stress hammer away at the immune system in the laboratory. Dr. Glaser of Ohio State and his wife, Dr. Janice Kiecolt-Glaser, found that small wounds took an average of nine days longer to heal in women who cared for patients with Alzheimer's disease than in women who were not under similar stress. In another study, arguments between husbands and wives were accompanied by increases in stress hormones and immunological changes over a 24-hour period.

Stress also seems to make people more likely to contract some infectious illnesses. Dr. Cohen of Carnegie Mellon has spent years inoculating intrepid volunteers with cold and influenza viruses, and his findings offer strong evidence that stressed people are more likely to become infected and had more severe symptoms after becoming ill.

A direct link between stress and more serious diseases, however, has been more difficult to establish, Dr. Cohen said. Recent studies have provided increased support for the notion that stress contributes to heart disease, and researchers have tied psychological stress, directly or indirectly, to diabetes,

rheumatoid arthritis, fibromyalgia, severe depression and other mental disorders. But the influence of chronic stress on other diseases like cancer remains controversial. All the same, Dr. Cohen said, "The evidence that stress puts people at risk for disease is a lot better than it was 10 years ago."

The Risks: From an Early Start, Lifelong Effects

Why do some people seem more vulnerable to life's pressures than others? Personality and health habits play a role. And severe stress in early life appears to cast a long shadow.

Dr. Michael Meaney of McGill University and his colleagues have found that rat pups intensively licked and groomed by their mothers were bolder and secreted lower levels of the stress hormone ACTH in stressful situations than rats lacking such attention - an equanimity that lasted throughout their lives. (Cuddled pups, the researchers found in another study, were also smarter than their neglected peers.)

In humans, physical and sexual abuse and other traumas in childhood have been associated with a more pronounced response to stress later in life. In one study, Dr. Charles Nemeroff, a psychiatrist at Emory University, and his colleagues found that women who were physically or sexually abused as children secreted more of two stress hormones in response to a mildly stressful situation than women who had not been abused.

Yet perhaps the best indicator of how people are likely to be affected by stress is their position in the social hierarchy. In subordinate male monkeys, for example, the stress of being servile to their alpha counterparts causes damage in the hippocampus. And dominant monkeys who are repeatedly moved from social group to social group, forcing them to constantly re-establish their position, also exhibit severe stress and are more likely to develop atherosclerosis, according to studies by Dr. Jay Kaplan of Wake Forest University School of Medicine.

Being low in the hierarchy also affects reproduction, presumably because evolution dictated that in times of stress, other factors were more pressing than procreation. In a recent study, Dr. Kaplan found that the constant low-level harassment by dominant female monkeys shut down reproductive function in subordinate females and built up fat deposits in their arteries.

It would be nice to think that humans are less chained to their social rankings. But alas, researchers have found this not to be the case. A wealth of studies shows that the risk for many diseases increases with every step down the socioeconomic scale, even when factors like smoking and access to health care are taken into account.

A real estate mogul living in a Park Avenue penthouse has a better health prognosis than the head of a small company in an upscale condo a few blocks away. And a renter in a one-bedroom apartment on the Upper West Side of Manhattan will be a tier or two lower still in health expectations.

Even people's perceptions of their relative standings in society affect their disease risk. In one study, led by Dr. Nancy E. Adler, also at the University of California at San Francisco, women who placed themselves higher on the social ladder reported better physical health and had lower resting cortisol levels and less abdominal fat than women who placed themselves on lower rungs.

No matter what one's circumstances, of course, some stress in life is inevitable. But illness is not, Dr. McEwen said. A variety of strategies can help reduce disease risk.

Reaching for a gallon of ice cream to soothe the tension of a family argument is not one of them, however, nor is forgoing exercise in favor of curling up on the sofa for an eight-hour marathon of "Law and Order."

The best ways to cope, Dr. McEwen said, turn out to be the time-honored ones: eat sensibly, get plenty of sleep, exercise regularly, stop at one martini and stay away from cigarettes. "It's a matter of making choices in your life," he said.

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