Understanding the Have-Knots

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"I can't express anger. I grow a tumor instead."
—Woody Allen

You live in a majorly stressed out world. You're never very far from a ringing cell phone or a guilt-inducing laptop. Traffic makes you flip out. And as if stressing out over lines, health, your job, your grades, or global terrorism wasn't enough, along comes the APS *Observer* with one more thing in your life to stress out over: *Stress*.

Stress, to put it bluntly, is bad for you. It can kill you, in fact. Medicine used to be skeptical that the mind could have a direct effect on the body, but any doubt of that has, alas, gone the way of the dinosaur or the relaxing weekend. Study after study now reveals that stress causes deterioration in everything from your gums to your heart and can make you more susceptible to everything from the common cold to cancer. The mind-body connection is real, and it is powerful, and thanks to new research crossing the disciplines of psychology, medicine, neuroscience, and genetics, the mechanisms underlying the connection are rapidly becoming understood.

Axis Powers

The first clues to the link between stress and health were provided in the 1930s by Hans Selye, the first scientist to apply the word "stress"— then simply an engineering term — to the strains experienced by living organisms in their struggles to adapt and cope with changing environments. One of Selye's major discoveries was that the stress hormone cortisol had a long-term effect on the health of rats. Cortisol has been considered one of the main culprits in the stress-illness connection, although it plays a necessary role in helping us cope with threats.

When an animal perceives danger, a system called the hypothalamic-pituitary-adrenal (or HPA) axis kicks into gear: A chain reaction of endocrine signals beginning in the hypothalamus results in the

release of various hormones — most notably epinephrine ("adrenaline"), norepinephrine, and cortisol — from the adrenal glands above each kidney. These hormones boost heart rate, increase respiration, and increase the availability of glucose (cellular fuel) in the blood, thereby enabling the famous "fight or flight" reaction. Because these responses take a lot of energy, cortisol simultaneously tells other costly physical processes — including digestion, reproduction, physical growth, and some aspects of the immune system — to shut or slow down.

The HPA axis is a self-regulating (homeostatic) mechanism, a lot like a thermostat. Stress hormones act back upon the hypothalamus to inhibit production of more signaling chemicals, thus causing less stress hormones to be released down the line. When occasions to fight or flee are infrequent and threats pass quickly, the body's stress thermostat adjusts accordingly: Cortisol levels return to baseline (it takes 40-60 minutes), the intestines resume digesting food, the sex organs kick back into gear, and the immune system resumes fighting infections. But problems occur when stresses don't let up — or when, for various reasons, the brain continually perceives stress even if it isn't really there.

Danger! Danger!

Stress begins with the perception of danger by the brain, and it appears that continued stress can actually bias the brain to perceive more danger by altering brain structures such as the medial prefrontal cortex (mPFC) and amygdala, which govern the perception of and response to threat. Prolonged exposure to cortisol inhibits the growth of new neurons in the mPFC, an area that ordinarily acts to inhibit the HPA axis, and can cause increased growth of the amygdala, the portion of the brain that controls fear and other emotional responses. The end result is heightened expectation of and attention to threats in the environment (see Fox et al., 2007).

Stress hormones also inhibit neuron growth in parts of the hippocampus, a brain area essential in forming new memories. In this way, stress results in memory impairments and impairs the brain's ability to put emotional memories in context (Sapolsky, 1994). Think of it this way: Too much stress and you forget not to be stressed out. These brain changes are thought by some researchers to be at the heart of the link between stress and depression — one of stress's most devastating health consequences — as well as posttraumatic stress disorder (PTSD).

The best known of stress's health impacts are on the heart. The idea that stress directly causes coronary heart disease has been around since the 1950s; although once controversial (or thought to be mediated solely by behavioral responses like smoking or overeating), the direct stress-cardiac link is now well-documented by many studies. For instance, men who faced chronic stresses at work or at home ran a 30 percent higher likelihood of dying over the course of a nine-year study; in another study, individuals reporting neglect, abuse, or other stressors in childhood were over three times as likely as nonstressed individuals to develop heart disease in adulthood (Miller & Blackwell, 2006).

Stress appears to be cumulative. Although when we think of stressors we might think of big things like abuse, illness, divorce, grieving, or getting fired, it is now known that the little things — traffic, workplace politics, noisy neighbors, a long line at the bank — can add up and have a similar impact on our well-being and our health. People who report more minor irritants in their lives also have more mental and physical health problems than those who encounter fewer hassles (Almeida, 2005). And recent research shows that PTSD may be the result of stressors adding up like building blocks, remodeling the plastic brain in a cumulative rather than a once-and-for-all fashion (Kolassa and Elbert,

2007).

To designate the cumulative wear and tear on physical systems due to long-term overactivation of the stress response, Rockefeller University neuroendocrinologist Bruce McEwen (1998) developed the concept of "allostatic load." Studies showing serious health consequences of allostatic load on the rest of the body's systems are numerous and growing. Besides heart disease, PTSD, and depression, chronic stress has been linked to ailments as diverse as intestinal problems, gum disease, erectile dysfunction, adult-onset diabetes, growth problems, and even cancer. Chronic rises in stress hormones have been shown to accelerate the growth of precancerous cells and tumors; they also lower the body's resistance to HIV and cancer-causing viruses like human papilloma virus (the precursor to cervical cancer in women; see Antoni & Lutgendorf, 2007).

Adding insult to injury, stress may even have a self-perpetuating effect. Depression and heart disease, for example, are not only the results of stress, but also causes of (more) stress. Consequently, the chronically stressed body can appear less like a thermostat than like a wailing speaker placed too close to a microphone — a feedback loop in which the stress response goes out of control, hastening physical decline with age.

Tuning the Stress Response

Growing evidence shows that our sensitivity to stress as adults is already "tuned," so to speak, in infancy. Specifically, the amount of stress encountered in early life sensitizes an organism to a certain level of adversity; high levels of early life stress may result in hypersensitivity to stress later, as well as to adult depression. A history of various stressors such as abuse and neglect in early life are a common feature of those with chronic depression in adulthood, for example (see Gillespie & Nemeroff, 2007).

At McGill University in Montreal, Michael J. Meaney and his colleagues have studied mother and infant rats, using rat maternal behavior as a model of early life stress and its later ramifications in humans. The key variable in the world of rat nurturance is licking and grooming. Offspring of rat mothers who naturally lick and groom their pups a lot are less easily startled as adults and show less fear of novel or threatening situations — in other words, less sensitivity to stress — than offspring of less nurturant mothers. The same thing is true of offspring of naturally less nurturant mothers who are raised (or "cross-fostered") by more nurturant ones. By the same token, low-licking-and-grooming rat mothers are themselves more fearful than the more nurturant rat moms; but again, female offspring of those non-nurturant mothers foster-parented by nurturant mothers show less fear and are themselves more nurturant when they have pups of their own. This indicates that the connection between maternal nurturance and stress responsiveness is not simply genetic, but that fearfulness and nurturance are transmitted from generation to generation through maternal behavior (Parent et al., 2005).

A mechanism responsible for this tuning of the stress response is found at the "top" part of the HPA axis. One of the signaling chemicals released by the hypothalamus in response to stress is called CRF (for corticotropin-releasing factor — so-named because its function is to tell the pituitary gland to release another hormone, corticotropin, or ACTH, which in turn signals the adrenal glands to kick into action). Adult rats who had been well licked and groomed as pups show inhibition of CRF receptors in the amygdala (Parent et al., 2005).

In its extreme form, the human equivalent of low licking and grooming is child abuse and neglect.

Research on abuse and neglect in humans and its connection to anxiety disorders, depression, and PTSD in later life shows the same CRF-mediated mechanism. Elevated levels of CRF are found in the cerebrospinal fluid of individuals with depression, and people who have committed suicide have been found to have changes in the frontal cortex consistent with chronic elevation of CRF (Gillespie & Nemeroff, 2007). More subtly, the degree of maternal care predicts trait anxiety and the responsiveness of an individual's HPA axis to stress. In one study, adult children of Holocaust survivors showed altered HPA response and higher PTSD incidence, indicating that responsiveness to stress can be transmitted behaviorally from generation to generation in humans, as in other animals (Yehuda et al., 2000).

A Good Response Gone Bad

The vicious cycle of stress hormones biasing us to perceive more threat and react with an increased stress response might seem like some kind perverse joke played by nature — or at least a serious design flaw in the brain. But it makes better sense if we take the brain out of its modern, urban, "civilized" context.

The stress response is a necessary response to danger. For animals, including most likely our hominid ancestors, behavioral transmission of individual differences in stress reactivity from parents to offspring makes sense as an adaptation to fluctuating levels of danger in the environment. Animals raised in chronically adverse conditions (e.g., high conflict, material deprivation) may expect more of the same in the near future; so in effect the maternal treatment of offspring attunes them to the level of stress they may expect to encounter in their lives (Parent et al., 2005). As such, a response that seems baffling and counterproductive in a modern, civilized context may make more sense in the context of our distant evolutionary past.

Even depression has been theorized as playing an adaptive role in certain contexts. The inactivity, lack of motivation, loss of interest in pleasurable activities like sex, and withdrawal from social relationships experienced by depressed people closely resemble "sickness behavior" — the energy-saving lethargy activated by the immune system in response to infection (see Miller & Blackwell, 2006). In a natural setting, the hopeless attitude of depression may be the most adaptive for an organism infected with a pathogen: The best strategy for survival is not to expend energy fruitlessly and become exposed to predators, but to hunker down, hide from threats, and direct energy to immune processes where it's needed.

According to Stanford neuroendocrinologist Robert Sapolsky, who has studied stress in baboon troops, it is the relative safety from predators and high amounts of leisure time enjoyed by some primates — including humans — that has transformed these useful biological coping mechanisms into a source of pointless suffering and illness (Sapolsky, 1994). (Yes, it turns out that baboons suffer from depression and other stress-related disorders, just like people do.)

Mind-Body Mechanisms

The great challenge in stress psychology — and the necessary precursor to developing interventions against stress's harmful effects — has been understanding the mechanisms by which thoughts and feelings and other "mental" stuff can affect bodily health. For many years, it was believed that the main causal link between stress and disease was the immune suppression that occurs when the body redirects its energy toward the fight-or-flight response. But recent research has revealed a far more nuanced picture. Stress is known to actually enhance one important immune response, inflammation, and

increasingly this is being seen as the go-between in various stress-related diseases.

Ordinarily, inflammation is how the healthy body deals with damaged tissue: Cells at the site of infections or injuries produce signaling chemicals called proinflammatory cytokines. These cytokines in turn attract other immune cells to the site, to help repair it. Cytokines also travel to the brain and activate the HPA axis, and they are responsible for initiating sickness behavior. Overactive cytokine production has been found to put individuals at greater risk for a variety of aging-related illnesses (Robles, Glaser, & Kiecolt-Glaser, 2005).

Cytokines may be an important mediator in the relationship between stress and heart disease. When the arteries feeding the heart are damaged, cytokines induce more blood flow, and thus more white blood cells, to the site. White blood cells accumulate in vessel walls and, over time, become engorged with cholesterol, becoming plaques; these may later become destabilized and rupture, causing heart attacks (Miller & Blackwell, 2006). Cytokine action also has been implicated in the link between stress and depression. People suffering from clinical depression have shown 40–50 percent higher concentrations of certain inflammatory cytokines. And about 50 percent of cancer patients whose immune responses are artificially boosted through the administration of cytokines show depressive symptoms.

The close connection between inflammation and both depression and heart disease has led some researchers to theorize that inflammation may be what mediates the two-way street between these two conditions: Depression can lead to heart disease, but heart disease also often leads to depression (Miller & Blackwell, 2006). Sleep may be part of this puzzle too, as disturbed sleep, which often goes with anxiety and depression, increases levels of proinflammatory cytokines in the body (Motivala & Irwin, 2007).

Stressed-Out Personalities

Not everyone responds the same way to stress. Personality traits like negativity, pessimism, and neuroticism are known to be risk factors for stress-related disease, as are anger and hostility.

In the late 1950s, Friedman and Rosenman (1959) identified a major link between stress and health with their research on the “Type A” personality: a person who is highly competitive, aggressive, and impatient. This personality was found to be a strong predictor of heart disease, and later research clarified the picture: The salient factors in the relationship between the Type A personality and health are mainly anger, hostility, and a socially dominant personality style (for example, tending to interrupt other people when they are talking; see Smith, 2006). When negative emotions like anger are chronic, it is as if the body is in a constant state of fight or flight (with the allostatic load this state entails).

There is now evidence that another trait associated with success-striving in the modern world — persistence — may also lead to health problems in some circumstances. When goals are not readily attainable, the inability to detach from them may produce frustration, exhaustion, rumination on failures, and lack of sleep. These in turn activate harmful inflammatory responses that can lead to illness and lowered immunity (Miller & Wrosch, 2007).

The bottom line: Woody Allen’s neurotic character who grows a tumor instead of releasing his anger isn’t far from the truth.

By the same token, studies have shown that optimistic people have lower incidence of heart disease, better prognosis after heart surgery, and longer life. The effects of a positive attitude on immunity were shown in a study by APS Fellow and Charter Member Sheldon Cohen, Carnegie Mellon University, and his colleagues, in which individuals were exposed to a cold virus in a laboratory setting and watched over six days. Those with a positive emotional style were less likely to develop colds than were individuals with low levels of positive affect (Cohen & Pressman, 2006). (Note that researchers like Cohen distinguish low levels of positive affect from negative affect — a low level of positive affect does not necessarily mean a high level of negative affect, and vice versa.) Positive affect was also found to be correlated with reduced symptom severity and reduced pain. Conscientiousness also has been found to predict longevity (see Smith, 2006). Cohen's research earned him APS's top honor, the James McKeen Cattell Award, in recognition of his contributions toward understanding the effects of social and environmental stress on human behavior and health and the impact of his research across a range of fields.

The Future: Behavioral Genetics

Personality and environmental factors are not the whole story when it comes to stress. The next frontier of stress research is the rapidly growing field of behavioral genetics. Modeling the interaction of genetic and environmental influences is no longer a matter of weighing the relative input of nature and nurture. The two intertwine in subtle and complicated ways, with environments affecting gene expression, and vice versa, throughout life. Thus, the current watchword is "stress-diathesis" models, in which environmental stressors have varying impact on individuals due to preexisting inherited vulnerabilities.

One major advance in this area was the discovery by APS Fellow and Charter Member Avshalom Caspi, University of Wisconsin, and his colleagues of a link between stress sensitivity and a particular gene called *5HTTLPR*. This gene controls a protein that regulates the amount of the neurotransmitter serotonin (5HTT) available in the synaptic cleft (space between neurons). Individuals possessing two "short" variants (or alleles) of this gene and who also had experienced five or more stressful life events were more likely to have a depressive episode than similarly stressed individuals who had two "long" alleles of the gene (Caspi et al., 2003). In other words, a certain genetic makeup seems to increase risk for a serious illness through the mechanism of increased sensitivity to stressful occurrences.

Nathan Fox, University of Maryland, and his colleagues subsequently reported that children with two short alleles of the *5HTTLPR* gene whose mothers also reported receiving low social support were more likely to show behavioral inhibition (fearfulness and a tendency to withdraw) at age 7. Those receiving high support did not show the tendency, and those with the long alleles but receiving low support also appeared "protected" by their genetic makeup. Behavioral inhibition may put a child at risk for mental illness in later life (Fox et al., 2007).

Genetic predisposition to stress sensitivity may in some cases become a self-fulfilling cycle. Fox and colleagues found that some very behaviorally inhibited children were regarded by their mothers as hard to soothe and received less care and sensitivity as a result; this in turn tuned up the child's sensitivity to stress through the alterations in the mPFC and amygdala mentioned earlier. In the model Fox and colleagues propose, genetically influenced temperament in early childhood influences the quality of caregiving children receive, which in turn shapes a child's attention bias to threat.

A Cup Half Full

So Nietzsche's strenuous view of life, "whatever doesn't kill me makes me stronger," just plain isn't true. Stressors that don't kill you in the short run may yet shorten your life or drastically lessen its quality.

But quit your moping and look on the bright side: The newly refined science of stress could lead to new drug therapies that can control stress or inhibit its effects on health. Also, depression and anxiety are not only results of stress, but also causes, and existing therapeutic and medical treatments for these conditions can help change how people perceive threats, put their life challenges in context, and cut stressors down to manageable size. The cycle doesn't have to be vicious, in other words.
What's more, the confirmation that the mind directly affects the body can work as much in our favor as it does to our detriment, as the personality-and-stress research above indicates. As APS Fellow Carol Dweck, Stanford University, has argued, personality is mutable (see Herbert, 2007); if our outlooks and beliefs about ourselves can be changed, so (theoretically) can our vulnerability to life's slings and arrows.

The bottom line: Stress is not inevitable. Even with more than one's fair share of vulnerability genes, there's plenty of room to take one's life and one's mind in a less stressful direction. Relaxation techniques such as meditation and yoga, for example, have been confirmed to quell stress demons. Even if you are a determined workaholic glued to your cell phone or a fearful and angry urban neurotic like Woody Allen, stress-reduction methods are readily available to cope with stress in the short term and even alter perceptions of stressors in the long term.

Meyer Friedman, co-discoverer of the link between "Type A" behavior and heart disease, is a case in point. A self-described Type-A personality, Friedman wound up suffering a heart-attack at age 55. He made the conscious choice to change his ways in accordance with his own discoveries — including following his own prescription by reading the classics. To get more in touch with his slow, patient, and creative side, he read Proust's languid seven-volume opus *Remembrance of Things Past* three times. In short, he trained himself to relax and enjoy life, and he had the last laugh at stress by living to the ripe old age of 90. ?