Founding Editor's Viewpoint

The Allostatic Load: How Stress Makes Us Sick

One of the most important elements in communities of scholars is an extensive dialogue between clinicians and molecular biologists. The latter study the mechanisms of disease in minute detail—stepping, as it were, into the living cell to explain how it produces the phenomena we observe in our patients who experience and endure disease. Several weeks ago, The Partnership for Gender-Specific Medicine at Columbia University brought together 11 scientists, foremost in their knowledge of how stress works to unhinge us and make us sick, in a groundbreaking conference, "Women, Men, and Stress: Gender-Specific Differences in Its Causes, Prevention, and Response to Intervention."

The expert faculty reminded us that despite all our investigative skills and ingenious techniques, some of the most relevant factors in the etiology of disease will always evade exact assessment. Stress is a prime example: How much is too much? What kind of emotional pain plays a significant role in making us sick? When does a stimulating challenge turn into a burden that is so intense and severe that it makes us ill? What factors go into making a resilient person who seems to endure life's most random, savage blows with equanimity and why are other, seemingly advantaged persons overwhelmed by minor disappointments? Dr. Bruce S. McEwen, Alfred E. Mirsky Professor of Neuroendocrinology at The Rockefeller University and probably the most important scholar working in this field, summarized it this way: "The body is hardly static; rather, blood pressure, heart rate, endocrine output, and neural activity are constantly changing across an operating range in response to environmental challenges....Pushing beyond this range can lead to disaster."[1]

McEwen and his protégées, Dr. Elizabeth Gould, Professor of Psychology at Princeton University, and Dr. Catherine Woolley, Professor of Neurobiology and Physiology at Northwestern University, explained how the brain responds to a challenge: far from being fixed in stone once we are adults, the brain is constantly changing. It makes new neurons to adapt to the flux in the world around us. Mediated by hormones and genetics, there are virtually instantaneous changes in neuronal receptor sensitivity and density, the level of neurotransmitters, and even the number of dendritic spines on individual cells in response to an environmental challenge. Thus, developmental age, hormones, and previous experience are all woven into a constellation of factors that make the individual response to stress unique—each animal, each person, has his or her own. The impact of early experience was particularly unexpected and perhaps one of the most poignant revelations of the conference. If animals, including humans, are inadequately handled and cared for during the first days of life, the nervous system is permanently altered. The result is an anxious, less emotionally competent adult less able to meet an environmental challenge.[2] The central roles of the hippocampus and the amygdala, communicating with the frontal cortex to fashion a response to stress, was striking—Dr. McEwen pointed out that prolonged, intense psychic pain could cause neuronal death in the hippocampus, which measurably shrinks under unrelenting strain. Successful handling of challenges actually augments hippocampal size.

The cardiologists among us were interested in the impact of stress on the heart. I have never treated a patient with coronary artery disease (CAD) who did not tell me that stress was a major cause of his or her disability. What causes emotional pain to men and women is gender specific: the same environmental factors present different changes to the two sexes, and the very nature of the cardiovascular response to stress is gender specific. Men have been found to have significantly higher systolic blood pressure at rest and higher elevations with stress ($P < 0.004$), and women have been reported to have a significantly higher heart rate at rest ($P < 0.02$) and to increase their heart rate with stress.[3] Men are "vascular reactors," while women are "cardiac reactors." The noxious rise in blood pressure with stress is most marked in

adolescent and young to middle-aged males; this may be one of the reasons for the much earlier onset of atherosclerotic heart disease in men compared with women.[4] In a study of 901 healthy and unmedicated Finnish men aged 42 to 60 years, blood pressure reactivity and carotid artery atherosclerosis were directly related only in the youngest half of the sample (46- to 52-year-old men).[5]

The perception of an environmental challenge is strikingly different for men and women. Wamala et al[6] have reported that women who have complex responsibilities outside of work, combined with low-status jobs over which they have relatively little control, have a 4-fold increased risk for CAD. Frankenhaeuser and colleagues'[7] observations about women, work, and the home noted that when men and women at the same occupational level crossed the threshold of their home, women's blood pressures and heart rates remained elevated, while that of men decreased. In contrast, the physical demands of men's work take a deadly toll: in a study of 612 Finnish middle-aged men, a third of whom were working at jobs in which the energetic demands exceeded the upper level of recommended aerobic strain, high energy consumption accelerated the progression of atherosclerosis,[8] the mechanism of which was probably a sustained increase in systolic blood pressure.[9]

Marital stress can be deadly for women with CAD: Wamala et al[6] found that such women had a 3-fold increased risk of a new coronary event compared with those who were unmarried or happily married. Men, on the other hand, experience mental stress primarily at work and rarely in the family situation.[10] Even more striking in contrast to women, marriage seems to provide health benefits for men. Single men with their first myocardial infarction were found to have a 2-fold increase in the risk of death compared with married men, and bereavement has been reported to have a greater effect on men than on women.[11]

Despite the interesting observations that work and personal relationships have a different impact on men and women, psychic pain is a uniquely individual phenomenon. As Elliott[12] and others have pointed out, the relationship of stress to CAD depends on the meaning of the situation to the individual. It is clear that if we want to care for patients with cardiovascular disease and, indeed, with illnesses of all kinds, we must understand that each person's experience of the world around him and its impact on his psyche is unique. At any given moment, his response is tempered by his genetics, hormones, age, and experience, particularly his early experience. Any animal can be overwhelmed if what McEwen has called the "allostatic load" is perpetuated. He warns that frequent stresses, a lack of adaptation to them, the inability to turn off compensatory mechanisms once the stress has passed, and the failure of some of the physiologic systems that maintain our equilibrium, triggering compensatory increases in others, can all overwhelm the patient and result in life-threatening disease.[13]

The most successful physician will understand his patient's limitations and assets and, in collaboration with the patient, fashion solutions for solving problems that initially seem overwhelming. If the patient can articulate the cause of his emotional pain, the most important therapeutic intervention we can make begins with the question: "What are you going to do about this?" Finding a solution in collaboration with the unique individual in our consulting room may be genuinely life saving.

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