### Douglas Hospital Research Centre Symposium Symposium du Centre de recherche de l'Hôpital Douglas

### Stressed or stressed out: What is the difference?

Bruce S. McEwen, PhD

Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY

The term "allostasis" has been coined to clarify ambiguities associated with the word "stress." Allostasis refers to the adaptive processes that maintain homeostasis through the production of mediators such as adrenalin, cortisol and other chemical messengers. These mediators of the stress response promote adaptation in the aftermath of acute stress, but they also contribute to allostatic overload, the wear and tear on the body and brain that result from being "stressed out." This conceptual framework has created a need to know how to improve the efficiency of the adaptive response to stressors while minimizing overactivity of the same systems, since such overactivity results in many of the common diseases of modern life. This framework has also helped to demystify the biology of stress by emphasizing the protective as well as the damaging effects of the body's attempts to cope with the challenges known as stressors.

On a forgé le mot «allostase» pour clarifier les ambiguïtés associées au mot «stress». Allostase s'entend des phénomènes d'adaptation qui maintiennent l'homéostase dans la production de médiateurs comme l'adrénaline, le cortisol et d'autres messagers chimiques. Ces médiateurs de la réponse au stress favorisent l'adaptation dans le sillage du stress aigu, mais ils contribuent aussi à la surcharge allostatique, à l'usure du corps et de l'esprit qui découle du fait d'être «stressé». Ce cadre conceptuel a créé le besoin de savoir améliorer l'efficience de la réponse d'adaptation aux facteurs de stress tout en réduisant au minimum la suractivité des mêmes systèmes puisque la dite suractivité cause un grand nombre des maladies courantes de la vie moderne. Ce cadre a aussi aidé à démystifier la biologie du stress en mettant l'accent sur les effets protecteurs et dommageables des efforts déployés par le corps pour faire face aux défis appelés facteurs de stress.

### Introduction

Stress is a constant factor in modern life and a frequent topic of conversation. As a *New York Times* columnist put it a few years ago, "Stress is a word that is as useful as a Visa card and as satisfying as a Coke. It's non-commital and also non-commitable." Yet in spite of its frequent use, the word "stress" is at best an ambiguous term. For some, it means excitement and challenge ("good stress"); for many others, it reflects an undesirable state of chronic fatigue, worry, frustration and inability to cope ("bad stress"). For this latter situation, I prefer the term "stressed out," which implies the chronic nature of a negative state. To allow more precision in the discussion of stress, my colleagues and I have introduced new terminology and a new conceptual framework focused

on the biologic mechanisms used in coping with stress and the central role of the brain. This new framework distinguishes between the protective and damaging consequences of the response to stressors.

Stressors of all varieties were initially thought to ignite a general and diffuse arousal reaction in the body.<sup>2</sup> Through the enormous progress that has been made in biomedicine over the past half century, a very different picture of integrative physiology has emerged — one in which the social environment has a cumulative impact on physical and mental health and the progression of a number of specific diseases. This effect of the social environment results from the fact that the brain and the body are in 2-way communication via the autonomic nervous system and the endocrine and immune systems. It is these systems that provide protection and allow

Correspondence to: Dr. Bruce S. McEwen, Laboratory of Neuroendocrinology, The Rockefeller University, 1230 York Ave., New York NY 10021; fax 212 327-8634; mcewen@rockefeller.edu

Medical subject headings: allostasis; allostatic overload; stress; adaptation, physiological; adaptation, behavioral; homeostasis.

Submitted Dec. 21, 2004; Revised June 8, 2005; Accepted June 13, 2005

© 2005 CMA Media Inc.

adaptation in the face of acute stress, yet they also contribute to the negative impact of chronic stress and an unhealthy lifestyle.<sup>3</sup> Thus, rather than "stress," an ambiguous term that has both good and bad connotations, what most people are most concerned with when they talk about stress is the state of being "stressed out."

I will begin by describing the concept of stress as defined by the late Canadian–Hungarian medical scientist Hans Selye, which is the basis for our work. I shall then introduce the new terminology and conceptual framework for understanding what it means to be "stressed out."

# New interpretation of Selye's general adaptation syndrome

Hans Selye (1907–1983) is credited with introducing the concept of stress into popular, as well as medical, discussions. Selye used the emergency reaction of the sympathetic nervous system and adrenocortical system for his classic theory of stress,² which is exemplified by the "fight or flight" response. Selye postulated the general adaptation syndrome, a stereotyped physiologic response that takes the form of a series of 3 stages in the reaction to a stressor. The first stage is the alarm reaction, in which the adrenal medulla releases epinephrine and the adrenal cortex produces glucocorticoids, both of which help to restore homeostasis. Restoration of homeostasis leads to the second stage, that of resistance, in which defence and adaptation are sustained and optimal. If the stressor persists, the stage of exhaustion follows, and adaptive response ceases; the consequence may be illness and death.

How has this view of stress changed in light of new information? First, Selye's general adaptation syndrome is no longer interpreted to mean that all types of stress evoke the same stereotyped response of the stress mediators. Rather, the hypothalamic-pituitary-adrenal (HPA) axis and the noradrenergic and adrenergic nerves have different patterns of response that are related to the type of stressor. 4 Second, the "fight or flight" response does not apply equally to both sexes; rather, it most accurately characterizes the response of male animals under threat. The female response to non-lifethreatening stress has been characterized as "tend-andbefriend," not "fight or flight." Thus, although females do flee from extreme danger, differences between the sexes must be factored in to any understanding of allostasis and allostatic load (see below for explanation of these terms). These differences include not only differing perceptions of and behavioural responses to stressors, but also physiologic differences in the regulation of mediators of the stress response. Furthermore, studies in male and female rodents have drawn attention to opposite reactions to acute tailshock restraint stress on classical conditioning: males show improved conditioning performance, whereas females show worse conditioning performance.6

## Allostasis and allostatic load: reinterpreting Selve

In addition to a change in interpretation of the general adap-

tation syndrome and recognition of differences between male and female responses, Selye's third stage, that of exhaustion, is particularly in need of reinterpretation in light of newer knowledge that the stress mediators can have both protective and damaging effects, depending on the time course of their secretion. Thus, rather than problems being caused by an exhaustion of defence mechanisms, it is the stress mediators themselves that can turn on the body and cause problems. Recognition of this effect has led my research team to develop a new terminology (and associated conceptual framework) for linking the protective and damaging effects of the biologic response to stressors, namely, "allostasis" and "allostatic overload." These 2 terms allow for a more restricted and precise definition of the overused word "stress" and provide a view of how the essential protective and adaptive effects of the physiologic mediators that maintain homeostasis are also involved in the cumulative effects of daily life when they are mismanaged or overused.

A central construct in Seyle's integrative model of stress was the notion of homeostasis, the stability of the physiologic systems that maintain life. My colleagues and I apply the concept of homeostasis only to a limited number of physiologic variables (end points), such as pH, body temperature, glucose levels and oxygen tension, that are truly essential for life and that are therefore maintained within a narrow range of their respective set-points. These set-points and other boundaries of control may themselves change with environmental conditions; however, these changes cannot be explained solely by the notion of homeostasis.

We have therefore introduced the concept of allostasis to refer to the superordinate system by which stability is achieved through change. Primary mediators of allostasis include, but are not confined to, hormones of the HPA axis, catecholamines and cytokines. Allostasis also clarifies the inherent ambiguity in the term "homeostasis" by distinguishing between the systems that are essential for life (homeostasis) and those that maintain these systems in balance (allostasis).

When set-points or other boundaries of control vary beyond the limits of homeostatic mechanisms, these variables are referred to as being in allostatic states. An allostatic state results in an imbalance of the primary mediators, reflecting excessive production of some and inadequate production of others. Some examples of allostatic states are chronic hypertension; a flattened cortisol rhythm in major depression or after chronic sleep deprivation; chronic elevation of inflammatory cytokines accompanied by low cortisol in chronic fatigue syndrome; and the lower cortisol, higher corticotropin-releasing factor and elevated cytokines in the Lewis rat, which are associated with increased risk for autoimmune and inflammatory disorders, relative to the Fischer rat.

Allostatic states can be sustained for limited periods if food intake or stored energy such as fat can fuel the homeostatic mechanisms (as is the case for bears and other hibernating animals preparing for winter). If the increased food intake continues, as would be the case for animals in captivity that have adequate energy reserves, then symptoms of allostatic overload appear.<sup>8</sup> Abdominal obesity is an example of this condition and is common in animals in zoos, as well

as in our own species. Allostatic states, therefore, refer to altered and sustained activity levels of the primary mediators (e.g., glucocorticosteroids) that integrate energetic and associated behaviours in response to changing environments and challenges such as social interactions, weather, disease, predators and pollution.

Allostatic states can produce wear and tear on the regulatory systems in the brain and body. The terms "allostatic load" and "allostatic overload" refer to the cumulative results of an allostatic state (e.g., fat deposition in a bear preparing for winter, a bird preparing to migrate or a fish preparing to spawn). Either of these can be considered the result of the daily and seasonal routines that organisms use to obtain food for survival and extra energy for migration, moulting, breeding and other seasonal activities. Within limits, these routines involve adaptive responses to seasonal and other demands. However, if the additional load of unpredictable events in the environment (e.g., storms, natural disasters), disease outbreaks, disturbances caused by humans and antagonistic social interactions is superimposed, then allostatic load can increase dramatically to become allostatic overload. Allostatic overload serves no useful purpose and predisposes the individual to disease.8

Thus, in the new terminology of allostasis, Selye's alarm response is reinterpreted as the process leading to adaptation, or allostasis, in which glucocorticoids and epinephrine, as well as other mediators, promote adaptation to the stressor. Selve's stage of resistance reflects the protective effects of the adaptation to the stressor. But if the alarm response is sustained and the adrenal output of glucocorticoids and catecholamines is repeatedly elevated over many days, an allostatic state may ensue, leading to allostatic overload, which replaces Selye's stage of exhaustion. Here, the important distinction must be made that this state represents the almost inevitable wear and tear produced by repeated exposure to mediators of allostasis, i.e., too much of a good thing. Thus, Selve's diseases of adaptation are the result of the allostatic state leading to allostatic overload and resulting in the exacerbation of pathophysiologic change.

#### Protection and damage

Every system of the body responds to acute challenge with allostasis leading to adaptation. When these acute responses are overused or inefficiently managed, allostatic overload results.

In the brain, secretion of the stress hormones adrenalin and cortisol in response to an acutely threatening event promotes and improves memory for the situation so that the individual can stay out of trouble in the future; however, when the stress is repeated over many weeks, some neurons atrophy and memory is impaired, whereas other neurons grow and fear is enhanced.<sup>9,10</sup>

In the immune system, acute stress promotes immune function by enhancing movement of immune cells to places in the body where they are needed to defend against a pathogen, yet chronic stress uses the same hormonal mediators to suppress immune function.<sup>11</sup>

In the cardiovascular system, getting out of bed in the morning requires an increase in blood pressure and a reapportioning of blood flow to the head to allow a person to stand up without fainting.<sup>12</sup> Blood pressure rises and falls during the day as physical and emotional demands change, providing adequate blood flow as needed. Yet repeated elevation of blood pressure promotes generation of atherosclerotic plaques, particularly when combined with metabolic factors that damage the coronary artery walls.<sup>13</sup>

For metabolism, glucocorticoids (so named because of their ability to promote conversion of protein and lipids to usable carbohydrates) serve the body well in the short run by replenishing energy reserves after a period of activity, like running away from a predator. Glucocorticoids also act on the brain to increase appetite for food and to increase locomotor activity and food-seeking behaviour,14 thus regulating behaviours that control energy input and expenditure. This effect is useful during manual labour or when playing active sports, but it is not beneficial when someone grabs a pizza and a beer while watching television or writing a paper, particularly when these activities may also be generating psychologic stress. Inactivity and lack of energy expenditure create a situation where chronic elevation of glucocorticoids, resulting from poor sleep, ongoing stress or as side effects of a rich diet, can impede the action of insulin to promote glucose uptake.15 Thus, whether it is psychologic stress or sleep deprivation or a rich diet that is increasing the levels of glucocorticoids, the consequences in terms of allostatic load are the same — insulin resistance and increased risk for cardiovascular disease.15

# Conclusions: involvement of mind and body in the state of being "stressed out"

For the purposes of this review, the "mind" includes not only what goes on in the brain but also the visceral sensations, including pain, as well as inflammatory states and many other processes that take place throughout the body. These components influence mood, attention and arousal and have effects on cognitive function. The examples of allostatic overload cited above — the acceleration of atherosclerosis and increased risk for cardiovascular disease and stroke, abdominal obesity — involve both the brain and the body, as do loss of minerals from bone, immunosuppression and alterations in the circuitry of the hippocampus, amygdala and prefrontal cortex, especially the hippocampus.<sup>10,16</sup> Many of these conditions are seen in patients with chronic mood and anxiety disorders, 17 and thus it is important to pay attention to the allostatic overload associated with these disorders, since they involve the whole body and not just the brain in isolation.

The final message, then, is that with new biomedical knowledge, the concept of stress has evolved from the ideas originally proposed by Hans Selye. Attention is now focused on how the mediators of the stress response can promote adaptation in the aftermath of acute stress and yet contribute to the allostatic overload that results from being "stressed out." This conceptual framework has created a need to know how to improve the efficiency of the adaptive response to stressors while

minimizing overactivity of these systems, since such overactivity results in many of the common diseases of modern life.

Competing interests: None declared.

#### References

- 1. Shweder R. America's latest export: a stressed-out world. *New York Times* 1997 Jan 26;Sect 4:5(col 1.)
- Selye H. A syndrome produced by diverse nocuous agents. Nature 1936;138:32.
- 3. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338:171-9.
- Goldstein DS, Eisenhofer G. Sympathetic nervous system physiology and pathophysiology in coping with the environment. In: McEwen BS, editor. Coping with the environment: neural and endocrine mechanisms. Vol. 4. New York: Oxford University Press; 2000. p. 21-43.
- Taylor SE, Klein LC, Lewis BP, Gruenewald TL, Gurung RAR, Updegraff JA. Biobehavioral responses to stress in females: tend-andbefriend, not fight-or-flight. *Psychol Rev* 2000;107:411-29.
- Wood GE, Shors TJ. Stress facilitates classical conditioning in males, but impairs classical conditioning in females through activational effects of ovarian hormones. *Proc Natl Acad Sci U S A* 1998;95:4066-71.
- Koob GF, LeMoal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 2001;24:97-129.

- McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Horm Behav 2003;43:2-15.
- Roozendaal B. Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology* 2000;25:213-38.
- McEwen BS. Structural plasticity of the adult brain: how animal models help us understand brain changes in depression and systemic disorders related to depression. *Dialogues Clin Neurosci* 2004;6:119-33.
- Dhabhar F, McEwen B. Enhancing versus suppressive effects of stress hormones on skin immune function. *Proc Natl Acad Sci U S A* 1999:96:1059-64.
- 12. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason J, editors. *Handbook of life stress, cognition and health*. New York: John Wiley & Sons; 1988. p. 629-49.
- Manuck SB, Kaplan JR, Adams MR, Clarkson TB. Studies of psychosocial influences on coronary artery atherogenesis in cynomolgus monkeys. *Health Psychol* 1988;7:113-24.
- 14. Leibowitz SF, Hoebel BG. Behavioral neuroscience of obesity. In: Bray GA, Bouchard C, James WPT, editors. *Handbook of obesity*. New York: Marcel Dekker; 1997. p. 313-58.
- Brindley D, Rolland Y. Possible connections between stress, diabetes, obesity, hypertension and altered lipoprotein metabolism that may result in atherosclerosis. Clin Sci 1989;77:453-61.
- Sapolsky RM. Why stress is bad for your brain. Science 1996;273:749-50.
- Evans DL, Charney DS. Mood disorders and medical illness: a major public health problem. Biol Psychiatry 2003;54:177-80.

Journal of Psychiatry & Neuroscience Revue de psychiatrie & de neuroscience

## Change of address

We require 6 to 8 weeks' notice to ensure uninterrupted service. Please send your current mailing label, new address and the effective date of change to:

### **CMA Member Service Centre**

1867 Alta Vista Dr. Ottawa ON K1G 3Y6

tel 888 855-2555 or 613 731-8610 x2307 fax 613 236-8864 cmamsc@cma.ca

### **Changement d'adresse**

Il nous faut de 6 à 8 semaines d'avis afin de vous assurer une livraison ininterrompue. Veuillez faire parvenir votre étiquette d'adresse actuelle, votre nouvelle adresse et la date de la prise d'effet du changement, à l'attention du

#### Centre des services aux membres de l'AMC

1867, prom. Alta Vista Ottawa ON K1G 3Y6

tél 888 855-2555 ou 613 731-8610 x2307 fax 613 236-8864 cmamsc@cma.ca

