CHAPTER

# 1

# Stress, Definitions, Mechanisms, and Effects Outlined: Lessons from Anxiety

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OUTLINE



## Abstract

The present volume on concepts, cognition, emotion, and behavior, is the first in this new *Handbook* series. The purpose of this first chapter is to provide an outline of stress, stress definitions, the response to stress and neuroendocrine mechanisms involved, and stress consequences such as anxiety and posttraumatic stress disorder. Study of the neurobiology of anxiety and related disorders has facilitated our understanding of the neural mechanisms that subserve stress and will therefore be underscored.

*Now is the age of anxiety* **W.H. Auden**

## INTRODUCTION

"Stress" has been dubbed the "Health Epidemic of the 21st Century" by the World Health Organization and is estimated to cost American businesses up to $300 billion a year. The effect of stress on our emotional and physical health can be devastating. In a recent US study, over 50% of individuals felt stress negatively impacted work productivity. Between 1983 and 2009, stress levels increased by 10-30% among all demographic groups in the United States.

Numerous studies show that job stress is by far the major source of stress for American adults and that it has escalated progressively over the past few decades. Increased levels of job stress as assessed by the perception of having little control but many demands have been demonstrated to be associated with increased rates of heart attack, hypertension, obesity, addiction, anxiety, depression, and other disorders. In New York, Los Angeles, and other municipalities, the relationship between job stress and heart attacks is recognized, so that any police officer who suffers a coronary event on or off the job is assumed to have a work-related injury and is compensated accordingly.

Stress is a highly personalized phenomenon that varies between people depending on individual vulnerability and resilience, and between different types of tasks. Thus one survey showed that having to complete paper work was more stressful for many police officers than the dangers associated with pursuing criminals. The severity of job stress depends on the magnitude of the demands that are being made and the individual's sense of control or decision-making latitude for dealing with the stress.

Stress is, of course, not limited to the workplace. There is vast literature on the possible role of stress in the causation and/or exacerbation of disease in most organ systems of the body. Inextricably linked to anxiety, stress plays a pivotal role in mental disorders including phobias, major depression, and bipolar disorder.[2–9] Stress and anxiety aggravate schizophrenia and people with schizophrenia often experience difficulties in coping with stress. Consequently, stress-inducing changes in lifestyle patterns place a substantial burden on mental health.

Posttraumatic stress disorder (PTSD) is a special form of stress that affects more than 7 million people in the United States. In 1980, largely as a consequence of the psychological trauma experienced by Vietnam War veterans, PTSD was recognized as a disorder with specific symptoms that could be reliably diagnosed and was, therefore, added to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). PTSD is recognized as a psychobiological mental disorder that can affect survivors of not only combat experience in war and conflict, but also terrorist attacks, natural disasters, serious accidents, assault, rape trauma syndrome, battered woman syndrome, child abuse syndrome, or sudden and major emotional losses. PTSD is associated with epigenetic changes in the brain as well as changes in brain function and structure. These changes provide clues to the origins and possible treatment, and prevention of PTSD. Stress, PTSD, and anxiety are linked to fear, fear memory and extinction, phenomena that together with their neural circuitry and neurochemistry remain the subject of intense research. Notwithstanding its links with anxiety, PTSD in the latest DSM-5 is now included in a new section/classification of trauma- and stressor-related disorders. This move of PTSD from its earlier classification in the DSM-IV as an anxiety disorder is among several changes approved for PTSD that heighten its profile as a disease entity that is increasingly at the center of public as well as professional attention.

Physiological and neurochemical approaches have elucidated the way in which stress is controlled by two major neuroendocrine systems, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenomedullary (SAM) limb of the autonomic nervous system (ANS). Our understanding of stress mechanisms in man and animals has benefited significantly from several recent quantum leaps in technology and knowledge. First, advances in molecular genetics (including optogenetics and chemogenetics), sequencing of the human genome and genomics[10] have increased the rigor and precision of our understanding of the molecular neurobiology of stress and its effects on mental state, behavior, and somatic systems. Secondly, through genomics we are also beginning to understand the genetic and epigenetic factors that play a role in susceptibility, vulnerability, and resilience to stress and the various components of the stress response. Thirdly, functional brain imaging has enhanced our understanding of the neurobiology of stress in the human.

Here we provide an outline of stress with the focus on stress definitions, the response to stress, and neuroendocrine and central neurobiological mechanisms involved, and stress consequences, such as anxiety and PTSD. The neurobiology of anxiety is underscored because it has heuristically facilitated our understanding of the neural mechanisms that subserve stress.

### KEY POINTS

- Stress is the (nonspecific) response of the body to any demand.[1]
- Stress consequences include anxiety, fear, depression, and PTSD. In addition, stress has adverse effects on other major mental disorders such as bipolar disorder and schizophrenia.
- Stress also has adverse effects on the cardiovascular, including the cerebrovascular system and other organ systems of the body.
- Stressors are perceived and processed by the brain which triggers the release of glucocorticoids (by way of the hypothalamic-pituitary-adrenocortical axis) and catecholamines (adrenaline and noradrenaline) by way of the sympathetic-adrenomedullary system (SAM).
- The glucocorticoids and the catecholamines act synergistically to raise blood glucose levels (by triggering the release of glucose from the liver) which facilitates the "flight or fight" response to stress, as does the ramp-up of cardiovascular output by the catecholamines. The rapid stress-induced release of the catecholamines also shunts blood from the skin and gut to the skeletal muscles.
- Central awareness of and response to stress, anxiety, and fear depends on extensive neural circuits that involve, for example, the amygdala, thalamus, hypothalamus, brain stem nuclei such as the locus coeruleus and the neocortex and limbic cortex.
- Our understanding of the neurobiology of stress has been enhanced by experimental, clinical, and human brain imaging studies of anxiety and other stress-related conditions.

## STRESS DEFINITIONS

Stress has a different meaning for different people under different conditions. A working definition of stress that fits many human situations is a condition in which an individual is aroused and made anxious by an uncontrollable aversive challenge—for example, stuck in heavy traffic on a motorway, a hostile employer, unpaid bills, or a

predator. Stress leads to a feeling of fear and anxiety. Depending on the circumstances, the fear response can lead to either *fight or flight*. The magnitude of the stress and its physiological consequences are influenced by the individual's perception of their ability to cope with the stressor.

Stress is difficult to define. As Hans Selye (the oft-called "Father of stress") opined, "Everyone knows what stress is, but nobody really knows." Selye's definition, "Stress is the nonspecific response of the body to any demand,"[1] is the most generic. This definition and Selye's stress-related concepts had several detractors which he systematically rebutted.[11] Other definitions are detailed by Fink.[3] Briefly, they include the following:

- "Perception of threat, with resulting anxiety discomfort, emotional tension, and difficulty in adjustment."
- "Stress occurs when environmental demands exceed one's perception of the ability to cope."
- In the group situation, lack of structure or loss of anchor "makes it difficult or impossible for the group to cope with the requirements of the situation. Leadership is missing and required for coping with the demands of the situation."
- For the sociologist, it is social disequilibrium, that is, disturbances in the social structure within which people live.
- A purely biological definition is that stress is any stimulus that will activate (i) the HPA system, thereby triggering the release of pituitary adrenocorticotropin (ACTH) and adrenal glucocorticoids and (ii) the SAM system with the consequent release of adrenaline and noradrenaline.
- In their seminal review "The Stressed Hippocampus, synaptic plasticity and lost memories," Kim and Diamond[12] suggest a three-component definition of stress that can be applied broadly across species and paradigms. First, stress requires heightened excitability or arousal, which can be operationally measured using electroencephalography, behavioral (motor) activity, or neurochemical (adrenaline, glucocorticoid) levels. Second, the experience must also be perceived as aversive. Third, there is lack of control. Having control over an aversive experience has a profound mitigating influence on how stressful the experience feels. The element of control (and "predictability") is the variable that ultimately determines the magnitude of the stress experience and the susceptibility of the individual to develop stress-induced behavioral and physiological sequelae.

Thus, the magnitude of neurocognitive stress ($S$) approximates to the product of:

- Excitability/arousal ($E$)
- Perceived aversiveness ($A$)
- Uncontrollability ($U$)

$$(S) = E \times A \times U$$

### But Is the Stress Response "Nonspecific" as Proposed by Hans Selye?

In a seminal paper, Pacak and Palkovits[13] challenged Selye's doctrine of nonspecificity of the stress response. They studied the similarities and differences between the neuroendocrine responses ("especially the sympathoadrenal and the sympathoneuronal systems and the hypothalamo-pituitary-adrenocortical axis") among five different stressors: immobilization, hemorrhage, cold exposure, pain, or hypoglycemia. With the exception of immobilization stress, these stressors also differed in their intensities. Pacak and Palkovits found heterogeneity of neuroendocrine responses to these stressors: each stressor had its own specific neurochemical "signature." By examining changes of Fos immunoreactivity in various brain regions upon exposure to different stressors, Pacak and Palkovits also investigated the central stressor-specific neuroendocrine pathways. In a separate study on the aortic response to stress, Navarro-Oliveira et al.[14] showed that the SAM, but not the hypothalamic-pituitary-adrenal axis, participates in the adaptive responses of the aorta to stress.

There is now substantial literature on the specificity of stressors. Selye's definition of stress holds but the term "nonspecific" might be redundant. That is, Selye's definition of stress might now read "Stress is the response of the body to any demand."

## FEAR VERSUS ANXIETY….WHAT ARE THE DIFFERENCES?

Stress is inextricably linked with fear and anxiety. Definitions of fear and anxiety vary greatly, and to an extent depend on subjective assessment. Nonetheless, in their seminal review, "What is anxiety disorder?", Craske and associates,[15] using Barlow's concepts, state; "anxiety is a future-oriented mood state associated with preparation for possible, upcoming negative events; and fear is an alarm response to present or imminent danger (real or perceived)." This view of human fear and anxiety is comparable to that in animals. "That is, anxiety corresponds to an animal's state during a potential predatory attack and fear corresponds to an animal's state during predator contact or imminent contact."

Table 1 shows the prototypes of self-report symptoms of fear, anxiety, and depression. The symptoms that represent prototypes of fear and anxiety lie at different places upon a continuum of responding. "Along such a continuum, symptoms of fear versus anxiety are likely

**TABLE 1** Prototype of Self-Report Symptoms of Fear, Anxiety, and Depression

| | Clusters[a] | | |
|---|---|---|---|
| | **Fear** | **Anxiety** | **Depression** |
| *Response-systems* | | | |
| Verbal-subjective | Thoughts of imminent threat | Thoughts of future threat | Thoughts of loss, failure[b] |
| Somato-visceral | Sympathetic arousal | Muscle tension | Energy loss[b] |
| Overt motor | Escape | Avoidance | Withdrawal[b] |

[a] *While represented as prototypes, fear and anxiety may be better represented as points along a continuum, with varying degrees of symptom overlap.*
[b] *More specifically, these features represent lack of positive affect, as represented by the absence of thoughts of success, the absence of energy, and the absence of desire to be with other people.*
*Reproduced with permission from Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE.* Depression and Anxiety. *John Wiley and Sons.*

to diverge and converge to varying degrees." For further details, the reader is referred to Craske et al.[15]

## BIOLOGICAL RESPONSE TO STRESS

The biological response to stress involves activation of three major interrelated systems. First, the stressor is perceived by sensory systems of the brain, which evaluate and compare the stressful challenge with the existing state and previous stress experience of the organism. Second, on detection of a stressful challenge to homeostasis, the brain activates the ANS which through the SAM system triggers a rapid release of the catecholamines, noradrenaline, and adrenaline. The catecholamines increase cardiac output and blood pressure, shunt blood from the skin and gut to skeletal muscle, and trigger the release of glucose from the liver into the blood stream. Third, the brain simultaneously activates the HPA axis which results in the release of adrenal glucocorticoids, cortisol in man and fish, and corticosterone in rodents.

Increased glucocorticoid levels enhance the organism's resistance and adaptation to stress. However, the precise mechanisms of this defensive action of glucocorticoids remain to be elucidated. Glucocorticoids act synergistically with adrenaline to increase blood glucose, thus ensuring energy supplies often needed to overcome the stress by facilitating *fight or flight*. Glucocorticoids are also potent inhibitors of the immune response and inflammation, moderating the production of prostaglandins and inflammatory cytokines. In a seminal review, Munck and associates[16] proposed "that stress-induced increases in glucocorticoid levels protect not against the source of stress itself, but rather against the body's normal reactions to stress, preventing those reactions from overshooting and themselves threatening homeostasis." Munck's hypothesis has retained its currency. Thus, for example, Zhang et al.[17] have reported that glucocorticoids inhibit lipopolysaccharide-induced myocardial inflammation. Munck's theory does not necessarily conflict with the fact that in the uninjured brain, basal or acutely elevated glucocorticoid levels increase synaptic plasticity and facilitate hippocampal dependent cognition whereas chronically elevated glucocorticoid levels impair synaptic plasticity and cognition, decrease neurogenesis and spine density, and cause dendritic atrophy.[7,18,19]

Glucocorticoid actions are mediated by two biochemically distinct receptors which bind the same ligand (cortisol in humans, corticosterone in rodents), albeit with differing affinities. While glucocorticoid receptors (GRs) are ubiquitously distributed, the location of mineralocorticoid receptors (MRs) is more discrete. However, both receptors are expressed at particularly high levels in limbic areas that are responsible for the modulation of the stress response.[20] As compared with GR, MR have a much greater affinity for cortisol/corticosterone and are, therefore, highly occupied even under basal (stress-free) conditions.[20] In contrast, GR become increasingly occupied as circulating glucocorticoid levels rise in response to stress. MR have been implicated in the appraisal process and onset of the stress response, while GR are involved in the mobilization of energy substrates and most stress-induced changes in behavior.

The latter includes anxiety-like behavior and facilitated learning and memory (in particular, consolidation of memories). Long-term GR activation is associated with deleterious effects on several cognitive functions.[6,21–23] These deleterious effects have been correlated with neuroarchitectural changes in several brain regions, including the hippocampus, prefrontal cortex, and amygdala that are also implicated in modulating the negative feedback control within the HPA.[23,24]

The amount of glucococorticoid available for cells is "micromanaged" by 11β-hydroxysteroid dehydrogenase (HSD-11β) enzymes of which there are two isoforms. First, HSD11B1 which reduces cortisone to the active hormone cortisol that activates GRs. Second, HSD11B2 which oxidizes cortisol to cortisone and prevents illicit activation of the MR.[25–29]

While elevated glucocorticoid levels characterize stress, high levels of glucocorticoids per se do not mimic stress. Of the several central neurochemical neurotransmitters involved in the stress response, attention has focused on the corticotropin releasing factor (CRF) peptide family (and especially the urocortins) as possible orchestrators of the stress response. For details of the CRF peptide family and their cognate receptors, readers are referred to several reviews.[4,30–34]

## Stress Neuroendocrinology Outlined

As mentioned above, stressors are perceived and processed by the sensory cortex which drives the hypothalamus by several pathways that include the thalamus and the limbic forebrain and hindbrain systems.[35,36] The hypothalamus triggers the release of glucocorticoids and the catecholamines, the primary stress hormones, by way of the paraventricular nuclei (PVN) in the case of the HPA and the PVN, lateral hypothalamus, arcuate, and brainstem nuclei in the case of the SAM system.[3,31,37–40] The amygdala, a prominent component of the limbic system that plays a key role in the evaluation of emotional events and formation of fearful memories, is a prime target of the neurochemical and hormonal mediators of stress. Clinical and experimental data have correlated changes in the structure/function of the amygdala with emotional disorders such as anxiety.[3,8,31,33,38]

The PVN is subject to differential activation by distinct neuronal pathways, depending on the quality and/or immediacy of the demand for an appropriate response.[41,42] Stressors such as hemorrhage, respiratory distress, or systemic inflammation, which represent an immediate threat to homeostasis, directly activate the PVN, bypassing cortical and limbic areas, by activation of somatic, visceral, or circumventricular sensory pathways.[43,44] Excitatory ascending pathways originating in the brainstem nuclei that convey noradrenergic inputs from the nucleus of tractus solitarius,[45–48] serotonergic inputs from the raphe nuclei,[49,50] or inputs from adjacent hypothalamic nuclei[42] are well positioned to receive visceral and autonomic inputs so as to evoke rapid neuroendocrine responses.

The hypothalamic control of the release of pituitary ACTH is mediated by the 41-amino acid residue neuropeptide CRF transported from PVN nerve terminals to the anterior pituitary gland by way of the hypophysial portal vessels.[51,52] The action of CRF is potentiated by the synergistic action of the nonapeptide, arginine vasopressin (AVP), which, like CRF, is synthesized in the PVN.[53] ACTH stimulates the secretion of adrenal glucocorticoids which have powerful metabolic effects that promote the stress response. Homeostasis within the HPA is maintained by a negative feedback system by which the adrenal glucocorticoids (the afferent limb) moderate ACTH synthesis and release (the efferent limb). Allostasis, that is, maintenance of constancy through change in HPA activity to cope with increased stress load is brought about by change in feedback set point. It must be stressed that in biology, "set point" is a conceptual construct rather than a precise structural entity.[31]

The major sites of glucocorticoid negative feedback are the PVN, where glucocorticoids inhibit CRF and AVP synthesis and release, and the pituitary gland, where they block the ACTH response to CRF and inhibit the synthesis of ACTH and its precursor, proopiomelanocortin. The limbic system of the brain, especially the hippocampus and amygdala, also plays a role in glucocorticoid negative feedback.[4,7,8,31,38,39,54]

Central control of the ANS involves the hypothalamic PVN together with various brainstem and limbic nuclei (caudal raphe, ventromedial and rostral ventrolateral medulla, the ventrolateral pontine tegmentum). The ANS plays the pivotal role in the early (immediate) response to stress. ANS action is mediated mainly by way of the release of noradenaline from nerve terminals and adrenaline from the chromaffin cells of the adrenal medulla.[40,55] Adrenaline and noradrenaline facilitate the stress response by triggering the synthesis and release of glucose from the liver into the blood stream, increasing the rate and force of cardiac contraction and shunting blood from the skin and the gastrointestinal system to the skeletal muscles.

## Central Neural Stress-Response Mechanisms

In addition to the two canonical neural outflow systems (ANS and HPA), the stress response involves central nuclei, such as the locus coeruleus (LC), the principle brain nucleus for the production of noradrenaline. Located in the pons, the LC and its noradrenergic projections to the forebrain play a key role in the central control of arousal, attention, and the response to stress. The LC receives afferents from the medial prefrontal cortex, cingulate gyrus, amygdala, hypothalamus, and raphe nuclei. In turn LC noradrenergic projections innervate the spinal cord, the brain stem, cerebellum, hypothalamus, the thalamic relay nuclei, the amygdala, hippocampus, and the neocortex. Noradrenaline released from the LC neuronal projections has an excitatory effect on most of the brain, inducing arousal and priming central neurons to stimulus-activation. Stress shifts LC noradrenergic cell firing, normally moderated by glutamatergic input, to a high tonic firing. This shift is mediated by CRF projections from the central amygdala and mediated by CRF-R1 receptors in the LC.[39] In turn, LC noradrenergic cells project to the basolateral amygdala (BLA), hippocampal CA1, and the dentate gyrus (DG) where noradrenaline released shortly after stress exposure, enhances excitability, promoting the encoding of stress-related information. Glutamatergic output from the BLA to the hippocampal DG is thought to provide a means to "emotionally tag" information processed in the hippocampus.[39] After cessation of the stress, the stress-induced enhancement in activity of the LC, the BLA, the DG, and CA1 is gradually reversed, resulting in a return to the pre-stress activity level. In the LC, the frequency of tonic firing is reduced by opiates that bind to κ- and μ-opioid receptors. In the BLA, the DG,

and CA1, these gradual normalizing effects are produced by glucocorticoids, presumably through GR-mediated gene-dependent cascades.[39]

## Amygdala: Pivotal Role in Fear, Memory, Attention, and Anxiety

Animal studies have shown that the amygdala receives sensory information rapidly through the sensory thalamus and more slowly and precisely (in terms of topography) through the sensory cortex.[56–58] The thalamic or cortical pathway can be used for simple sensory stimuli such as those typically used in animal conditioning. Brain imaging findings on the role of the human amygdala in fear learning are consistent with those in animal models. As assessed by functional magnetic resonance imaging, fear conditioning in humans results in an increased blood-oxygen-level-dependent (BOLD) signal in the amygdala.[59,60] The magnitude of this BOLD response is predictive of the strength of the conditioned response.[60,61] In addition, a subliminally presented conditioned stimulus (CS)—one presented so quickly that subjects are unaware of its presentation—leads to coactivation of the amygdala and the superior colliculus and pulvinar.[62]

The pivotal role of the amygdala in the response to fear is underscored by the effects of brain lesions, in that patients in which the amygdala has been lesioned show no conditioned fear. However, providing the hippocampus is intact, these patients are able explicitly to recollect and report the events of fear conditioning procedures.[63–65] In contrast, bilateral lesions of the hippocampus that spare the amygdala, impair the ability consciously to report the events of fear conditioning, although there is normal expression of conditioned fear as assessed physiologically by skin conduction responses.[63] This dissociation following amygdala or hippocampal damage between indirect physiological assessments of the conditioned fear response (amygdala dependent) and awareness of the aversive properties of the CS (hippocampal dependent) supports the proposition that there are multiple systems for the encoding and expression of emotional learning in the human.

The amygdala, in addition to modulating memory systems, also alters processing in cortical systems involved in attention and perception and thereby potentially influences downstream cognitive functions both by direct projections and possibly also by way of the nucleus basalis of Meynert (NBM) that receives afferents from the central nucleus of the amygdala.[66] The NMB projects widely to the cortical sensory-processing regions. The NBM projections release acetylcholine, which has been shown to facilitate neuronal responsivity.[67,68] Transitory modulation of cortical regions by the amygdala might increase cortical attention and vigilance in situations of danger.[69–71] This view receives support from brain imaging that showed amygdala activation to fearful (versus neutral) faces does not depend on subjects' awareness of the presentation of the faces,[72] or whether or not the faces are the focus of attention.[73–75] These studies indicate that the amygdala responds to a fear stimulus automatically and prior to awareness.

The bed nucleus of the stria terminalis (BNST), considered to be an extension of the amygdala,[76] receives dense projections from the BLA, and projects in turn to hypothalamic and brainstem target areas that mediate autonomic and behavioral responses to aversive or threatening stimuli. The BNST participates in certain types of anxiety and stress responses and seems to mediate slower-onset, longer-lasting responses that frequently accompany sustained threats, and that may persist even after threat termination.[76,77]

In summary, a combination of lesion and imaging studies have shown that transitory feedback from the human amygdala to sensory cortical regions can facilitate attention and perception. The amygdala's influence on cortical sensory plasticity may also result in enhanced perception for stimuli that have acquired emotional properties through learning. By influencing attention and perception, the amygdala modulates the gateway of information processing. The amygdala enables preferential processing of stimuli that are emotional and potentially threatening, thus assuring that information of importance to the organism is more likely to influence behavior.

# CONCLUSIONS AND RELEVANCE FOR STRESS AND ANXIETY MANAGEMENT

The neurobiology of stress and anxiety has highlighted new potential therapeutic targets for the management of anxiety. There has been considerable investment, for example, into new strategies such as the design and development of central CRF receptors antagonists. Furthermore, much ongoing research is focused on cognitive-behavioral (e.g., exposure) therapy, as well as possible pharmacological fear extinction. Care obviously needs to be taken to avoid "conditional reinstatement." Reinstatement of extinguished fear can be triggered by exposure to conditional as well as unconditional aversive stimuli, and this may help to explain why relapse is common following clinical extinction therapy in humans.[78] Neuropharmacologically we know that noradrenergic augmentation in the amygdala following retrieval of a traumatic memory enhances memory reconsolidation and makes the memory less susceptible to fear extinction. Elevated noradrenergic activity is associated with persistence and severity of PTSD symptoms. That is, noradrenergic-modulated reconsolidation processes contribute to the maintenance and exacerbation of trauma-related memories in PTSD.[79] These and other factors that

need to be considered in devising management strategies for stress and its consequences, especially anxiety, PTSD and depression, will be covered in detail in specialist chapters in this and subsequent volumes of the *Handbook of Stress* series.

## Glossary

**Allostasis** Homeostasis, "stability through constancy" is maintained by a self-limiting process involving negative feedback control by the output variable, which in the case of the HPA, is the secretion of adrenal glucocorticoids. The limits of feedback control are set by a notional regulatory "set point."[31] Sterling and Eyer[81] introduced the term Allostasis, "stability through change" brought about by central nervous regulation of the set points that adjust physiological parameters in anticipation to meet the stress/challenge. McEwen[82] integrated the concept of *allostasis* to describe the adaptation process of the organism in the face of different stressors and different circumstances. That is, allostasis incorporates circadian, circannual, and other life-history changes that might affect the animal's "internal balance."

**Allostatic load** Allostatic load represents the cumulative impact of stressors on the body's physiological systems over the life course.[83] That is, allostatic load can be defined as the "long-term cost of allostasis that accumulates over time and reflects the accumulation of damage that can lead to pathological states." Allostatic load has been shown to predict various health outcomes in longitudinal studies, such as declines in physical and cognitive functioning, and cardiovascular morbidity and mortality. Allostatic load is measured using a point scale that combines a series of stress biomarkers of cardiovascular, immune, and metabolic function.[84,85]

**Homeostasis** Aristotle, Hippocrates, and the other Ancients were aware of stress and its adverse effects. However, Claude Bernard was the first to formally explain how cells and tissues in multicelled organisms might be protected from stress. Bernard, working in Paris during the second half of the nineteenth century, first pointed out (1859) that the internal medium of the living organism is not merely a vehicle for carrying nourishment to cells. Rather, "it is the fixity of the milieu intérieur which is the condition of free and independent life." That is, cells are surrounded by an internal medium that buffers changes in acid-base, gaseous ($O_2$ and $CO_2$) and ion concentrations and other biochemical modalities to minimize changes around biologically determined set points, thereby providing a steady state. Fifty years later, Walter Bradford Cannon, working at Harvard, suggested the designation *homeostasis* (from the Greek homoios, or similar, and stasis, or position) for the coordinated physiological processes that maintain most of the steady states in the organism. Cannon popularized the concept of "homeostasis" in his 1932 book, *Wisdom of the Body*.[80]

**Fight or flight** Walter Cannon also coined the term *fight or flight* to describe an animal's response to threat. This concept proposed that animals react to threats with a general discharge of the sympathetic nervous system, priming the animal for fighting or fleeing.

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