

**REVIEW**

# Neurophysiology of stress – from historical to modern approach

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**Summary**

Stress is present in our everyday lives and it is considered to be the driving force of evolution. Anxiety, chronic worries and panic attacks are the most common consequences of long-term and exhausting stress. The most significant fundamental contribution that is crucial for the development of the modern concept of stress was made by Claude Bernard who proposed the theory that the body was constantly maintaining a stable and well-balanced internal environment or “*milieu interieur*”. Maintaining the internal environment constant was defined as homeostasis by Cannon who proposed two maintenance mechanisms - through negative feedback from the autonomic nervous system and through sensory organs.

Hans Selye proposed stress as non-specific strain on the body, caused by an altered body function which is followed by the release of stress hormones. He named this process the general adaptation syndrome which had three stages: alarm reaction, initial phase exhibiting “fight or flight” response; resistance, when body is getting used to being stressed, and exhaustion, when resistance to stress is gradually decreased and collapses. Hans Selye was the first to coin the term “heterostasis” representing the procedure by which a new stable state was achieved by the activation of physiological adaptive mechanisms.

Lazarus highlighted emotions as an important factor in behavior in response to stress and provided a description of various reactions to stressors. He emphasized the process of cognitive assessment as a mediator in dealing with stressors - how a person imagines or evaluates an event in order to understand stress reactions in people. Eustress, considered to be positive stress leads to toned emotions, motivation and focused energy, while distress, negative stress, occurs after prolonged stress that exceeds our ability to deal with it. Distress causes anxiety or withdrawal (depression and anxiety), and is accompanied by unpleasant feelings and reduced work ability leading to mental and physical illnesses.

**Keywords:** neurophysiology, stress, history, hormones

**Stress is a non-specific reaction of the body to any request. Stress in health and disease is medically, socio-logically, philosophically the most important topic for humanity that I can imagine.**

**Hans Selye (1907–1982)**

## INTRODUCTION

Stress is present in our everyday lives and it is considered to be the driving force of evolution. The term stress did not exist in physiology literature 100 years ago, unlike most popular definitions that describe purely psychological reactions to stress. Before the term stress began to be used as a psychological term, it had been used to describe different types of physical exertion. The word stress is derived from the Latin words “*strictus*”, meaning tight or narrow and “*stringere*”, the verb meaning to tighten (1).

Up to 80% of patients’ visits to physicians are due to stress-related health issues (2). In other words, anxiety, together with chronic worries and panic attacks, is the most common consequence of long-term and exhausting stress (Figure 1). Almost all scientific discussions in biological and social sciences, including chemistry, genetics, endocrinology, neuroscience, epidemiology, psychiatry, psychology, etc., recognize a common history of stress in physiology (3).

## STRESS RESEARCH BEFORE HANS SELYE

### Claude Bernard (1865 -1961)

French physiologist Claude Bernard, one of the world’s greatest physiologists and the father of experimental medicine, made the most significant contribution which is crucial for the development of the modern concept of

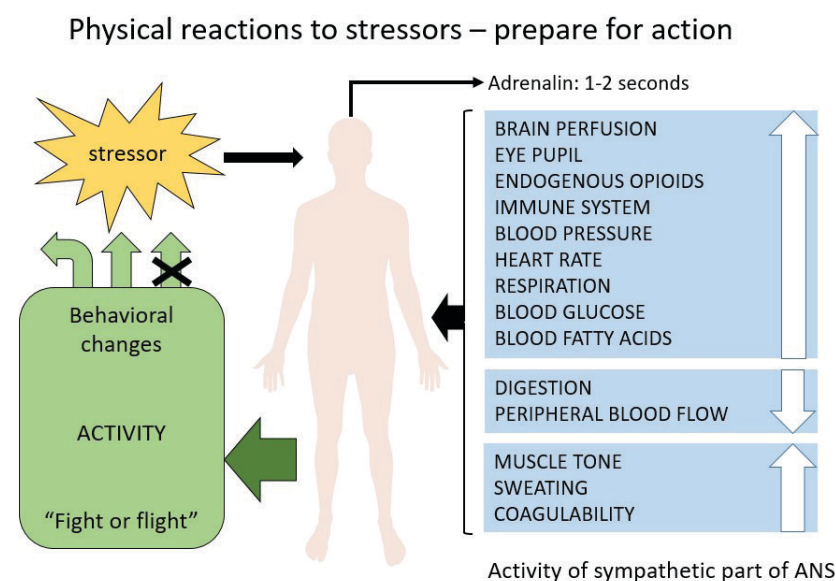
stress. Additionally, he explained how cells and tissues in multicellular organisms can be protected from stress. One of the most significant contributions was Bernard’s theory that the body was constantly working to maintain a stable and well-balanced internal environment or “*milieu interieur*”. In any stressful situation, the organism is tending to go back to its homeostatic state in order to coordinate physiological processes (4).

### Walter Bradford Cannon (1871–1945)

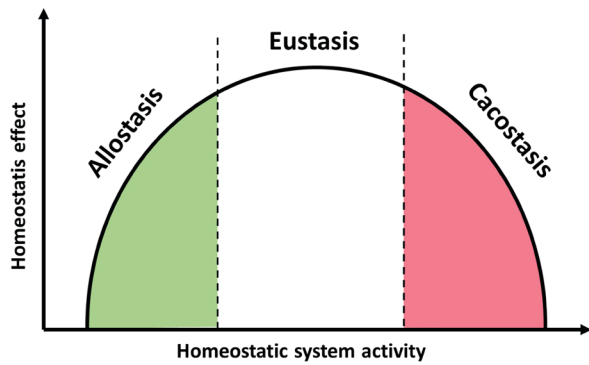
An American physiologist (Harvard Medical School) accepted the Bernard’s idea and expanded the theory (5). Cannon defined the process of maintaining the internal environment constant as “homeostasis” and proposed two maintenance mechanisms: through negative feedback via the autonomic nervous system activation and through sensory organs (6). The term homeostasis originated from the Greek roots *homoios* (similar) and *stasis* (stable). Walter Cannon created the term “fight-or-flight” to describe an animal’s reaction to a threat, which is called an acute stress response. In fact, the adaptive response to stressors triggers the activation of excitement and the sympathetic nervous system which leads to increased secretion of catecholamine (adrenaline) preparing the animal to fight the threat or save its life (i.e. flee) (7). He focused his own research on the specific and mutual relationship between stress and changes in the mind and body.

### Yerkes-Dodson (Robert M. Yerkes and John Dillingham Dodson, 1908)

Yerkes-Dodson’s law refers to the relationship between increased levels of arousal (used as a synonym for stress) and physiological and mental responses. Dodson’s law is represented by the inverse U-shaped curve for the optimal level of stress necessary to fight or give up the inten-



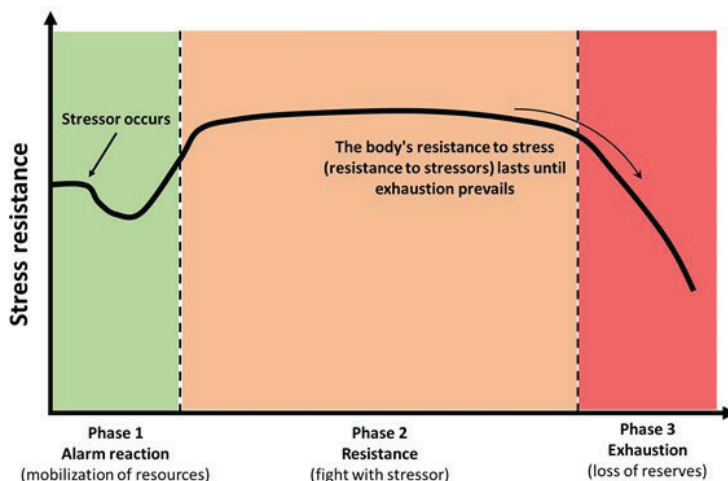
**Figure 1.** Stress represents physical and emotional adaptive response to internal and external stimuli



**Figure 2.** Yerkes-Dodson law (Inverted U-shaped curve): The relationship between stress level and task performance

tion. There is an optimal level of stress for each type of task that supports maximum effectiveness. This point (level) depends on individual characteristics, the type of stressor, the nature of the task itself, perception, etc. In most areas of life, it is necessary to have adequate energy, discipline and motivation. The relationship between these factors is linear only up to a certain point, because when the stress level becomes too high, the activity level (the effect) decreases (8) (Figure 2).

Work performance deteriorates when stress levels are too high or too low for a particular task. Having no stress at all causes motivation loss, a decrease in attention and interest for work. On the other hand, in the presence of too much stress, when the optimal point is crossed (across the border), the contribution is reduced and the work is counterproductive (9).



**Figure 3.** Three phases of Selye's general adaptation syndrome

BIOLOGICAL SYNDROME: STRESS	
<b>Phase</b>	<b>Neuroendocrine effect</b>
<b>Alarm reaction</b>	Activation of central nervous system
<b>Resistance</b>	Activation of hypothalamus-hypophysis-adrenal axis
<b>Tissue changes</b>	Adrenal gland hypertrophy, gastric ulcer, atrophy of thymus and lymphoid tissue
<b>Exhaustion</b>	Summation of effects and possible lethal outcome

## MODERN CONCEPT OF STRESS

### Hans Hugo Bruno Selye (1907–1982)

Hans Selye developed the concept of general adaptation syndrome (GAS), which was later called the stress response (10). Known as the “father of stress”, Selye began his research while a medical student (1926) because he noticed that many patients with various diseases had the same “non-specific” symptoms that were common responses to stress stimuli. The term “stress” has been accepted in all languages and it describes a “nonspecific neuroendocrine response” (11). Hans Selye published over 1,500 articles and 30 books on the subject of stress.

Selye described stress as nonspecific, since the reaction to stress can be a result of various types of stressors which made him focus on intrinsic, physical aspects of stress. Chronic stress causes excessive production of mediators, chemical substances and hormones, which can lead to gastric and duodenal ulcers and hypertension. Although the hypothesis of GAS later proved to be incorrect, he put stress on the map of the diseases and emphasized that stress had significant effects on the immune system, as well as on the adrenal gland (12).

By studying the physiology and pathology of stress and disease adaptation, he concluded that a certain amount of stress had positive effects, while too much stress led to pathological conditions, increasing autonomic and hormonal activity as well as muscle effort.

According to Selye, the critical task is to identify optimal levels of stimulation in the work environment. GAS has three phases: 1. alarm reaction; 2. adaptation; 3. exhaustion for a given stimulus (Figure 3). After exposure

to stressors, the alarm is initial response to stress which refers to the fight-or-flight effect, when the sympathetic nervous system is activated by a sudden release of hormones. Because no organism can be continuously in an alarm state, a phase of adaptation or resistance follows during which symptoms subside. The third phase or the phase of exhaustion occurs after an even greater and prolonged exposure to stressors, because the adaptability or “adaptive energy” of the organism is limited, and body is no longer able to cope with stress (13).

According to Selye, many stress-induced diseases occur in the resistance phase and according to him, these are “adaptation diseases”. These adaptive diseases include headache, insomnia, and increased blood pressure which carries a risk of heart dysfunction. Besides, there is an increased usage of chemical resources and increased immune response that can cause permanent changes in the body as well as kidney disease. Hans Selye was the first to coin the term “heterostasis” (from the Greek *heteros* or other) as the procedure in which a new stable state was achieved by the activation of physiological adaptive mechanisms (14-16).

### Heterostasis (cacostasis or allostasis)

Life and vital homeostatic systems (physiological) are programmed and rigorously adjusted during evolution, aiming to preserve a predefined steady state in order to maintain complex dynamic balance (homeostasis or eustasis) (17).

Stress leads to an imbalance of homeostasis or brings the organism into a state of disharmony. The adaptive response to stress is a new level of homeostasis that tends to correct and restore disturbed variables to their physiological range (18, 19).

The tendency to establish endangered homeostasis is called cacostasis or allostasis. Allostasis is homeostasis in the period of coping with stress under changed conditions. Allostasis provides stability and balance through psychological and behavioral changes. Optimal adjustment in the shortest period occurs by increasing hormone levels (20).

Homeostatic mechanisms exert their effects in the form of an inverse U-shaped curve in relation to the intensity of stress (homeostasis imbalance). Based on the homeostatic capacities of individuals homeostasis can be positioned at the following levels:

1. Basal homeostasis (or eustasis) is achieved in the central, optimal range of the curve, the organism returns to basal homeostasis or eustasis (Figure 4).
2. Suboptimal effects of homeostatic mechanisms may occur on both sides of the curve showing insufficient adaptation, allostasis
3. When adaptive responses are inadequate due to excessive, long-term exposure to stressors, the organism falls into cacostasis (improper homeostasis, dyshomeostasis), which can be harmful to the organism. Exposure to stressors (insufficient maternal care, poor family relationships, abuse, etc.) during critical periods of development when sensitivity to stressors is increased, such as periods of prenatal development, infant period, the periods of childhood and adolescence, can have long-lasting effects. Long-term cacostasis can last a lifetime because it is caused by an epigenetic plastic change in nerve cells (at the molecular level) that is induced by stress hormones (corticotropin releasing hormone and cortisol) and thus a weak brain response to stress.
4. The most favorable is hyperstasis or perfect adaptation of the organism, which is a consequence of improved homeostatic capacities based on experience. During the mentioned critical periods when cacostasis can be induced, individuals in a favorable social environment (understanding, care and concern of the mother for the offspring, etc.) develop resistance to stressors that will appear in adulthood by inducing hyperstasis. Epigenetics refers to the connection of man with environmental factors (exposure to psychosocial stress) in critical periods of growth and development that strengthens a child for stress in adulthood (21-23).

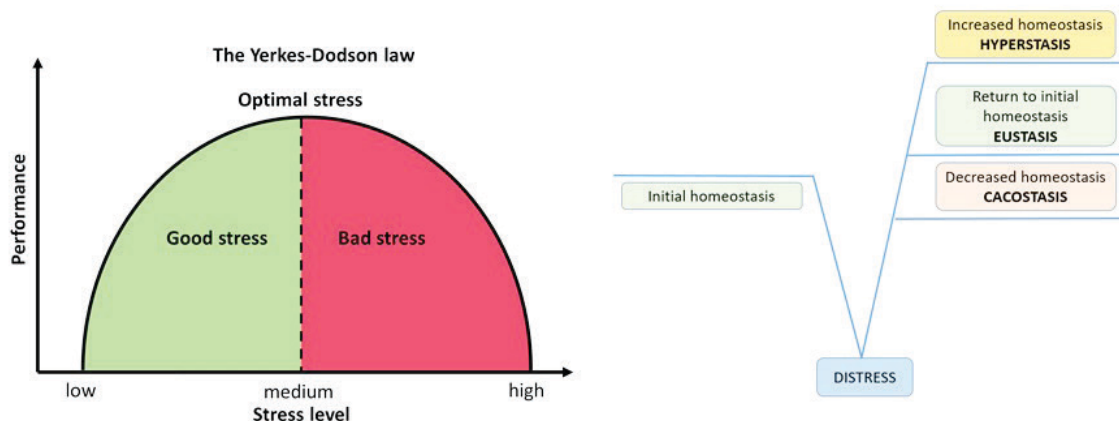


Figure 4. Activity of homeostatic systems: allostasis, eustasis, cacostasis and hyperstasis

## Richard Lazarus (1922–2002)

Lazarus R., one of the most influential psychologists in the history of this field, has an important role in the improvement of stress research with an attempt to find a theory that would consider several factors involved in the “stress response”. Lazarus (1966) argues that psychological stress occurs in individuals who consider the situation or circumstances as threatening. He emphasizes the process of cognitive assessment as a mediator in dealing with stressors - how a person thinks about or evaluates an event (information processing), in order to understand stress reactions in people (24, 25). The events themselves do not create stress, but the stress itself occurs after a cognitive evaluation and consideration of the event as threatening or negative (psychological stress). The basic assumption was that stress and coping with stress are reciprocal, because if coping is effective, stress is controlled and vice versa when coping is not effective, stress increases and can get out of control. Lazarus emphasized emotions as an important factor in behavioral response to stress and explained various reactions to stressors (26, 27).

### Positive (eustress) and negative (distress) stress

**Eustress** is considered to be positive stress because important life changes, such as marriage, the birth of a baby, a demanding job or retirement are not stress-free. Eustress is the stress that enhances physical or mental functions, helps achieving goals, increases excitement, concentration and performance, leading to personal progress as well as to effective avoidance of dangerous situations. The consequences of positive stress are toned emotions, motivation and focused energy (28, 29).

At birth, a child experiences one of the greatest stressful experiences in life. High levels of hormones released during birth affect the newborn’s adaptation to life outside the womb. Positive toned emotions in stress by artists (painters, composers, writers) or scientists are inspiring and creative. Positive attitude and good social support are strongly correlated with an increased ability of the immune system to fight pathogens. Optimists have good solutions to problems and use such experiences in dealing with chronic stressors (30, 31).

**Distress** is negative stress, created by the influence of prolonged stress that exceeds our ability to deal with it by coping or adapting (28). Negative stress causes anxiety or withdrawal (depression and anxiety), and is accompanied by unpleasant feelings, reduced work ability leading to mental and physical illnesses (32). Recent studies indicated that anxiety-related behavior in rats can also be enhanced by a lack of sleep and sleep deprivation, which can be considered as stress (33, 34). Besides, it has been showed that sleep deprivation can even make brain more susceptible to seizures by changing brain production of interleukins (35). In addition, chronic pain syndrome, as a stressful condition,

contributes to anxiety-like behavior that significantly correlates with brain biochemical and hippocampal immunohistochemical alterations (36). Stress can be the reason for the onset of a disease, but the disease for whose onset stress is the main reason is called stress disease.

## CONCLUSION

It is very complicated to define stress using simple terms - it simply represents a straining force in physical and mental manner. The concept of stress evolved over time depending on the specific period in history.

The modern concept of stress was based on Seyle’s principles or arguing against them. The effects of stress are the results of a complex interaction between environmental and genetic factors. Adaptation on everyday challenges and stressful events is individual and it depends on the previous stressful experiences, comorbidities, allostatic states and ability to cope and to maintain interior balance and psychical and emotional homeostasis. In modern age, stress is considered to be an important contributor to diseases, especially to cardiovascular and immune system disorders. New evidence supports the opinion that negative emotions, chronic pain or asleep disorders can lead to a psychiatric pathological condition such as anxiety, depression and emotional distress in general.

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### Authors’ contributions

OS conceptualized the manuscript. MV, DM, OS, ARM, DH did literature screening. NS, AZ and MV prepared figures. All authors participated in manuscript writing and provided critical intellectual inputs.

### Declaration of conflicting interests

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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## NEUROFIZIOLOGIJA STRESA – OD ISTORIJSKOG KA SAVREMENOM PRISTUPU

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### Sažetak

Stres je prisutan u svakodnevnom životu i smatra se pokretačkom snagom evolucije. Anksioznost, hronične brige, napadi panike najčešće su posledice dugotrajnog i iscrpljujućeg stresa. Najznačajniji fundamentalni doprinos koji je ključan za razvoj savremenog koncepta stresa dao je Klod Bernar predloživši teoriju prema kojoj telo stalno održava stabilno i dobro izbalansirano unutrašnje okruženje ili „*milieu interieur*“. Održavanje konstantne unutrašnje sredine Valter Kanon je definisao kao homeostazu i predložio dva mehanizma održavanja, putem negativne povratne sprege iz autonomnog nervnog sistema i preko čulnih organa.

Hans Seli je opisao stres kao nespecifično opterećenje za telo, uzrokovano izmenjenom funkcijom organa praćenom oslobađanjem hormona stresa. On je to nazvao opšti adaptacioni sindrom koji je imao tri stadijuma: alarmna reakcija, početna faza „bori se ili beži“; otpor-

nost, kada se telo navikava na stres i iscrpljenost kada se otpor prema stresu postepeno smanjuje i kolabira. Hans Seli je prvi skovao termin „heterostaza“ koji predstavlja postupak kojim se aktiviranjem fizioloških adaptivnih mehanizama postiže novo stabilno stanje.

Ričard Lazarus je istakao emocije kao važan faktor u ponašanju kao odgovor na stres i opisao različite reakcije na stresore. On naglašava proces kognitivne procene kao posrednika u suočavanju sa stresorima – kako osoba razmišlja ili ocenjuje neki događaj da bi razumeo reakcije na stres kod ljudi. Eustres, koji se smatra pozitivnim stresom, dovodi do toniranih emocija, motivacije i fokusirane energije, dok distres, negativni stres, nastaje nakon dužeg stresa koji prevazilazi našu sposobnost da se nosimo sa njim. Distres izaziva anksioznost ili depresiju, a praćen je neprijatnim osećanjima, smanjenom radnom sposobnošću koja dovodi do psihičkih i fizičkih bolesti.

**Ključne reči:** neurofiziologija, stres, istorija, hormoni

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