https://doi.org/10.17816/ecogen174103-111

ABOUT STRESS, … OR ABOUT HANS SELYE'S TWO ERRORS, CONQUERED THE WORLD

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Cite this article as: Daev EV.
About stress, … or about Hans Selye's two errors, conquered the world
Ecological genetics. 2019;17(4):103-111. https://doi.org/10.17816/ecogen174103-111.

Received: *05.12.2019* Revised: *12.12.2019* Accepted: *17.12.2019*

❀ Too broad understanding of the term "stress", which Selye himself and his followers used in their popular science works, reduces its scientific value. Based on a brief analysis of examples of the ambiguity of the term "stress", it is proposed to restore its research significance. For that, the concept of "stress" should be used more strictly and unequivocally and it would not be allowed to use a "commonly broad" understanding the term in scientific papers. In the frame of earlier Selye's stress definition, it suggests a more detailed structuring of the term based on levels of studying of living objects, including genetic.

❀ **Keywords:** stress; stressor; nonspecific response; general adaptive syndrome; "stress resistance"; terminology; term evolution.

О «СТРЕССЕ», … ИЛИ О ДВУХ ОШИБКАХ ГАНСА СЕЛЬЕ, ЗАВОЕВАВШИХ МИР

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Для цитирования: Даев Е.В. О «стрессе», … или о двух ошибках Ганса Селье, завоевавших мир // Экологическая генетика. – 2019. – Т. 17. – № 4. – С. 103–111. https://doi.org/10.17816/ecogen174103-111.

Поступила: *05.11.2019* Одобрена: *12.12.2019* Принята: *17.12.2019*

❀ Неоправданно широкое понимание термина «стресс», которое использовал в своих научно-популярных работах как сам Селье, так и его последователи, снижает его научную ценность. На основе краткого анализа примеров неоднозначности содержания термина предлагается вернуть ему исследовательскую значимость. Для этого в научных работах следует более строго и однозначно использовать понятие «стресс» и не допускать его «популистски широкого» понимания. В рамках ранних определений термина Гансом Селье предлагается более детальное структурирование по уровням организации живых объектов, включая генетический.

❀ **Ключевые слова:** стресс; стрессор; неспецифический ответ; общий адаптационный синдром; «стрессоустойчивость»; терминология; эволюция термина.

"Here the motto should be 'simplicity' and 'accuracy' … We should prefer a term that contains its own explanation …"

(Selye, "From Dream to Discovery," 1987)

The term "stress" is common in ecology research [1–3]. At the same time, the idea of stress in biology remains a problematic concept as it is "too widely used, insufficiently defined and sometimes even undesirable" [1]. From an environmental perspective, this is the internal state of an organism when it falls beyond the framework of its customary ecological niche [2].

The discussion of stress and the ambiguity of its interpretation in the biological sciences should be examined, beginning with Hans Hugo Bruno Selye (1907–1982).

Hans Selye is a Canadian scientist of Austro-Hungarian ancestry and is known as a researcher of the general adaptation syndrome (GAS) and the author of the universal concept of stress. In the early 1930s, he emigrated from Germany to the United States and then to Canada. A small note in the magazine *Nature* (1936) can be considered the onset of the appearance of the biomedical paradigm about the GAS [4].

The GAS phenomenon or stress response (stress), as a response to environmental pressures reaching a critical state, arose based on the ideas of Claude Bernard [5], which were developed further in the works of Walter Cannon [6, 7]. Living organisms, especially highly developed ones, must have a "mechanism for the maintenance of a constant and free life, independent of variations in the ambient cosmic environment." In fact, according to Bernard, the life of animals and plants was maintained through the energy balance determined by the nutritional balance of the body [5].

Despite the importance of the proposed physiological concept, its development continued more than half a century later [8]. In Cannon's works, the stable state of a living organism, whose parameters may fluctuate within certain limits, is called homeostasis. Beyond these limits, maintaining homeostasis is impossible, irreversible changes occur, and the organism eventually dies [6, 7].

In his work, Cannon used the terms "stress" and "strain" in a physical sense. The basis for this idea was its similarity to the processes occurring during material deformation. The increasing pressure on some material, within certain limits, causes elastic deformation, which is reversible and completely eliminated when the acting force is eliminated. The increase in pressure above a critical limit leads to plastic deformation, that is, to structural changes in the material. Such repeated changes, or a further increase in pressure, lead to material fatigue, the loss of some of its properties, and brittleness.

Similar processes occur in a living organism. Constant adaptation to changing environmental conditions changes the body itself, which is the stage of elastic and reversible deformation. If the strength or frequency of change exceeds a critical level, the body's reserves are depleted, leading to fatigue. With continued transcendental effects, brittleness occurs and the body eventually dies. Breakage of the material leads to fatal damage to homeostatic mechanisms and the death of the body after the depletion of all protective reserves [9]. Nevertheless, before the death of the organism, there is an intermediate stage in which the organism undergoes plastic deformation. When this occurs, part of its property changes become irreversible, and the organism remains alive but in an altered condition. Environmental changes lead to the body's inability to maintain homeostasis as they cause a number of side effects. Moreover, highly organized animals have much more complex mechanisms to respond to critical exposures, which include the elimination of damage incurred, adaptation to repetitive influences, and behavioral reactions to avoid the acting factor, etc.

"I have taken so many of Cannon's ideas! I can't do anything about it, I can only feel gratitude for this," Selye wrote in his book "From Dream to Discovery" [10]. Selye proposed his concept of stress by justifying and developing Cannon's ideas. In addition to a specific, sometimes local, response within the homeostatic capabilities of the body, the latter responds to critical influences with a nonspecific stereotypic reaction, which Selye called the GAS, stress response, or stress.

"Stress is a state of nonspecific tension in living matter, which is manifested by real morphological changes in various organs and, especially, in the endocrine glands controlled by the anterior lobe of the hypophysis" [11]. The syndrome develops in three stages with the initial emergence of acute symptoms, the anxiety stage, their subsequent disappearance, the resistance stage, and, finally, damage to the body with a complete loss of resistance [4, 11, 12]. Stressors, or the factors that induce a stress reaction, are varied in nature, but the response to them has a number of common characteristics, including the hypertrophy of the adrenal cortex, gastrointestinal ulcers, involution of the thymic–lymphatic apparatus, lymphopenia, inhibition of the thyroid function, inhibition of gonadotropin production, and suppression of the reproductive function in animals [12]. In fact, Selye lists the characteristics of stress, which were later termed "distress." The tension of the hypothalamic–pituitary–adrenal system is a characteristic feature of a stress syndrome, which "manifests itself in the body in two ways, damage and protection." Stress "as a whole seems to represent a generalised [*sic*] effort of the organism to adapt itself to new conditions" [4]. In this case, it is of great adaptive importance that the stimulation of the adrenal cortex goes indirectly through the anterior

Table 1

Equivalence of terms with "physical" and "biological" meanings

Item description	Area of research	
	Physics	Biology–Medicine
Acting factor	"Stress"	"Stressor"
Nonspecific organism response	"Strain"	"Strain"»

lobe of hypophysis, which partly helps to neutralize the harmful changes to the body [11]. As aforementioned, this is the content and relevance of the terms "stress" and "stressor," according to H. Selye [4, 11–14]. The scientific importance of Selye's discovery was that he noticed the lack of specificity of the body's response complex to various stressors.

Mammals, insects, and even unicellular organisms have a nonspecific response to external influences. Therefore, the extension of the term to all living organisms is apt, but the particular mechanisms of the stress response, nonspecific for each group of related organisms, become specific when comparing unrelated taxa, and the term stress will assume new meaning. It is impossible to imagine the presence, for example, the hypothalamic–pituitary–adrenal system in bacteria. Nevertheless, they have a nonspecific response to different factors. Therefore, the latter may be called "stressors" or "stressful events." Moreover, contemporary molecular biological studies indicate that a genome is involved in the formation of any response of an organism to external influences, whose activity changes are adaptations to new conditions. However, if adaptation is impossible within the limits of genome capabilities and is beyond the scope of a normal reaction for the genotype, or beyond its usual ecological niche [15], stress begins in the cells.

Genomic stress should be considered a component of cell stress and is accompanied by structural rearrangements of the genome, which may lead to the disintegration and death of the whole organism [16–20]. Thus, both the restructuring of the cellular genome and its damage in response to the stressor action is an initial stage of stress at the genomic level, which manifests itself at the physical level only when the number of damaged cells exceeds the acceptable level. However, this level is yet to be determined.

Selye undoubtedly considered parallelism in the staged nature of the response of some physical materials as well as the response of a living organism to external influences. Furthermore, the word "stress" was borrowed from the field of physics by both Cannon and Selye. For physicists, stress is the force (pressure) applied to an object, causing interior strain. Here Selye, a well-regarded scientific researcher, committed a semantic error that had lasting effects. He, being an emigrant of Austro-Hungarian descent with a working knowledge of English, wrote about "[t]he stress of life" in his book [21], that when defined the concept of stress, due to his level of English, the nuances of the terms stress and strain eluded him (Table 1).

"I would like to define here that the concepts of 'stress' and 'strain' in physics are similar to the terms 'stressor' and 'stress' in biology and medicine, respectively," he wrote [21].

The consequences of this error were obvious, as specialists in biology and medicine have often used the term in its physical sense, that is, as a stressor or stressor action [22]. For example:

"Physical stresses that are encountered rarely in populations – such as periods of drought or extreme cold or … in populations that are … exposed to local chemical stresses arising from human activities – can, through their direct or indirect effects, lead to …" [23].

"Environmental stresses such as extreme temperatures, dehydration and food deprivation may have distinct consequences …" [24].

This error demonstrates that the authors of these biological articles do not distinguish between stress and stressors. Rather, they use the term in a physical sense or demonstrate the varied interpretations of stress. Furthermore, the authors describe biological and specific effects, which is not stress. However, in scientific writing, the use of the term should be consistent.

Let the following example be indicative of this:

"***Stress*** may be defined as ***a relationship*** between an organism and external or internal factors that act to disrupt homeostasis. Organisms have evolved to have a variety of ***stress response pathways*** to mitigate the detrimental effects of stress to restore homeostasis. However, if the internal or ***external stress*** exceeds an organism's ***stress resistance*** capacity, this can lead to negative consequences … resistance ***to multiple forms of stress*** decline … [and] genetic mutants often exhibit increased resistance to ***various stresses***. For example, …exhibit high resistance to heat, oxidative, osmotic, hypoxic, ultraviolet, and heavy metal stresses" [25].

First, the original [26] states that stress is a particular relationship between a person and his environment, where he realizes a lack of his own resources that threaten his well-being. The meaning of the term becomes smeared, as this relationship occurs when a person is aware of a threat to his well-being. Researchers have little practical benefit to such vague definitions of stress.

Second, "external stress exceeds" and other highlighted places in the given publication [25] clearly indicate stressors.

Third, the use of the expression various stresses and the diversity of stress response paths contradicts the most important aspect of Selye's concept, namely, the nonspecific protective reaction or the GAS. This occurs when comparing nonspecific responses in organisms phylogenetically distant from one another.

The terms "stress resistance" and "stress sensitivity" are used frequently in the scientific literature. However, do these words reflect what the researchers are studying? How should we understand, for example, a report title from the Russian National Conference in 2019: "Stress resistance caused by stress at an early age"? If stress is an adaptively significant response of an organism, according to Selye, then what does resistance to this response indicate? To be more precise, this refers to the stressor resistance of the body, where it had already developed, but the stress reaction was interrupted due to the termination of the stressor action, for example.

What does it mean to be resistant or sensitive to one's own protective reaction (i. e., stress), to not respond to its development, or to not develop it? If we adhere to Selye's logic, it seems that the term "stress resistance," as well as "stress sensitivity," is used incorrectly, even meaningless. From a biological perspective, there appears to be a lack of consistency, which has become widespread as biologists, physicians, and psychologists participate in the incorrect use of such terms. Selye wrote about this, stating: "…that [it] is a mental error that deserves special attention, which in our laboratory we call the 'exaggerated authority of the generalized name'" [10].

Here, data from the Global Organization for Stress prove useful [27], as nine of the ten definitions of stress given by scientific stress researchers interpreted the term as the body's response options. Only one researcher discussed stress as an acting factor. Therefore, how may we come to understand why in biological works the term stress is so often used as a factor?

When developing his ideas about stress, Selye proceeded to make sweeping generalizations, defining stress as "a nonspecific response of the body to any demand made to it … [e]ven in a state of complete relaxation … a person experiences some stress. The heart continues to pump blood, the intestines continue to digest yesterday's dinner, and the respiratory muscles provide movement of the chest … Complete freedom from stress means death" [14]. Thus, he again confirmed his statement that "stress is life and life is stress." However, linking the concept of stress with life, Selye contradicts himself. The nonspecificity of biological stress syndrome, or the GAS, in higher animals is reductive to the three phases described above. Moreover, the first stage, anxiety, arises as a result of an insufficient capacity of the body to resist external influences and is characterized by pathological changes [14, p. 34–35]. If this is life, then it is not normal. Rather, it is a life under the conditions of stress. In his scientific work, Selye severely limited the meaning of the term to a nonspecific reaction of the body to critical influences that disrupt the body's homeostasis through characteristic symptoms (as was the case in earlier works that were not classified as popular science). He insisted on the correct use of the terms "stressor" and "stress." Then, the need for the separation of stress into "eustress," or favorable stress, and "distress," or unfavorable stress, would not arise, as stress could occur, and life would remain ordinary and normal. In addition, distress can be emphasized as a stage in which negative effects on the body are manifested. However, there is no eustress or favorable stress: there is just life.

The causes of stress (i. e. stressors), if necessary, can be placed into positive and negative categories. However, if both trigger stress, then this remains to be negative for the body.

When the body has already mobilized its evolutionarily ancient nonspecific adaptation mechanisms (resistance stage), and the action of the stressor has ceased, the body will be more protected when a new stressor appears. However, the positive action of the first stressor has manifested only in the case of the emergence of the subsequent stressful event. Is it necessary to compress another effect into the concept of stress, dividing it into eu- and di- prefixes? Researchers, especially psychologists, may discuss the positive and negative stressors, or causes thereof, but a stressor remains a stressor. If it does not disappear, then stress caused by a positive influence could induce death. Moreover, Alexander Pushkin illuminated this idea in the tale of "The Dead Princess and the Seven Knights," in which the princess could not tolerate admiration and died by the mass.

Since forming the response of an organism to external influences, nonspecific, within the limits of the relevant organisms, protective mechanisms may be activated, and the use of the term "stress" with regard to bacteria or plants holds. For example, participants of nonspecific protective reactions in bacteria are some polyamines (putrescine and spermidine) and heat shock proteins (HSPs) [28], and in plants, they are abscisic acid, dehydrins, and HSP families [29]. Concerning the problematic expansion of ideas about stress, this concept loses its specificity, which reduces the scientific value of the term [30].

If I were to say, "Let's study stress," invoking Selye's earlier definitions of the term, my statement would hold. However, if I invoke the more recent and widespread meaning of the term, this will not have any scientific value.

Hans Selye, a remarkable scientist and science communicator, likely underestimated the significance of his latest theoretical works and their impact on readers. Moreover, it was necessary to maintain rigor in the definitions of terms. Sometimes, perhaps, metaphorical statements about stress and life reach a wide readership and, unfortunately, are not always appropriately interpreted by readers. It was the reader who was influenced by the "exaggerated authority of the generalized name" created by the enthusiastic researcher and science communicator. The underestimation of the influence of his metaphorical definitions was Selye's second mistake.

The value of Selye's initial works consisted of an explicit restriction and a precise description of a nonspecific complex of phenomena that were revealed by him, namely, the GAS or stress. The followers of his work, as well as himself (see "response to stress" [31]), applied much effort to blur the boundaries of the phenomenon. This is all the more surprising since Selye considered simplicity, accuracy, thoroughness, and apprehensibility, as well as the correct use of a term, as necessary attributes of any term [10].

When transferring scientific information to a broad audience, and in translating scientific information from one language to another, the ambiguity of the content of ordinary words and special terms increases, causing distortions. The accuracy of the transfer of meaning in different forms (colloquial, textual, etc.) between people of different and even the same specialties may decrease significantly [32–34]. Therefore, in discussing research in the field of stress, authors are forced to stipulate on the duality of this term [29]. This approach to science is inconsistent and contradictory, and such an approach should be discarded. In science, especially in the scientific-educational process, phenomena, facts, and ideas "...should be expressed in terms that everyone can understand – not just teachers, educational researchers and scientists but also parents and others concerned with students' education" [35].

To strengthen the accuracy and specificity of the terms used in the study of stress in scientific papers, the following is advisable:

1. Adhere to clear limits in the use of the term "stress" as only a complex of nonspecific forms of response (that is, the GAS) to the stressor action (Fig. 1).

2. Call the factor causing the activation of nonspecific protective mechanisms of a living organism a stressor and not stress. Under certain circumstances, any factor can become or cease to be a stressor.

3. The term "distress," if at all necessary in the lexicon, should be used only as a stage in the development of the stress response. In biological works, do not use the term "stress" in the physical sense. Since the GAS can change the limits of the body's resistance, or the norm of a genotype reaction, to the action of stressors, the duration of the resistance stage may change. This coincides with the ideas of van Straalen [15].

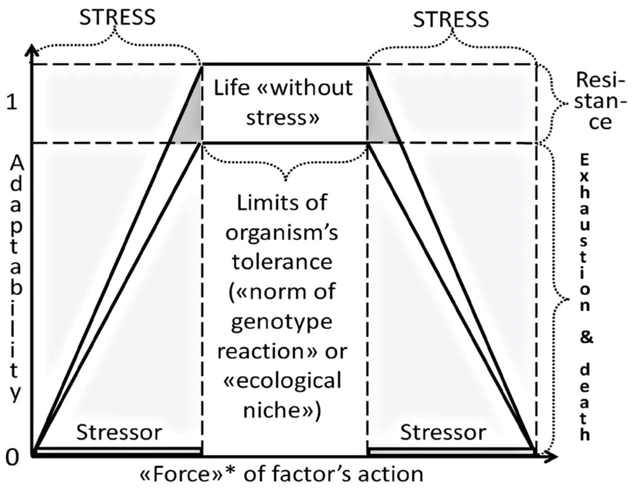

Fig. 1. Scheme about "stress" as general response of organism to environmental stressors. * force in that case means any action feature (duration, repeatability, intensity, absence of factor, etc.), which is out of common adaptability limits determined by evolution. Essential rearrangement of organism state in "stress" can change its resistance limits to stressor [15] – "norm of reaction". That leads to lasting resistance (often with reduced level of general fitness). The end of stressor action results in the same effect (or leads to restore of an organism properties)

4. In scientific articles, the use of the terms "stress resistance" and "stress sensitivity" as incorrectly reflective of the essence of the biological research being performed should be avoided.

5. The division of terms at the organization level of studied systems should be introduced. For example, cellular stress (SC) or C-GAS, with the entire complex of nonspecific cellular responses to stressors, stress of an organism (SO) or O-GAS, with all nonspecific responses at the organism level, stress of a population (SP) or P-GAS, etc.

Undoubtedly, with the development of any science, the conceptual apparatus used by it must evolve accordingly. Thus, the meaning of the term "stress," originating in physics and moving to biology, has acquired a new meaning. A deeper understanding of molecular biological processes has led to an expansion in the use of the term in relation to plants and bacteria, not only at the organismic level but also at the cellular and population levels. The data of molecular genetic studies have indicated the need to consider nonspecific responses to external influences at the genomic level. And at each

Table 2

Brief current elaboration of the term "stress" of living organisms depending on the research at definite level

Level	Stress abbreviation	Features of stress	
Cell*	SC	Nonspecificity of the response (GAS***)	ER-stress, ROS-stress, changes of HSPs, cell membranes, structural genome rearrangements, etc.
Organism**	SO		Works of H. Selye (Selye, 1936; 1950; 1975) and many others contain all main characteristics of stress
Population	SP		Reduced general fitness, declined density, abnormal behavior, changes in aging, sex and genetic structure, other changes

Note. *If necessary, SC of unicellular and multicellular organisms should be separated. ** Inside SO, if necessary, it is possible to separate stresses a tissue or an organ. Also it is possible to distinguish SO (or SP) of plants (SO-P or SP-P), insects (SO-I or SP-I) etc, in accordance with the generally accepted classification of living organisms, if "nonspecific" stress-reactions (within taxon, class, etc.) have their own specificity in comparison with other groups. *** general adaptation syndrome (GAS) should be understood as an attempt to cope with the "challenges" of the environment, as Selye wrote in 1936 [4], and this attempt goes beyond the normal functioning of the body.

level, there is a complex of characteristics of a nonspecific response (Table 2). Therefore, further evolution of both the content of concepts and their structure seems probable and necessary. Each of these terms — SC, SO, and SP — should be further structured and detailed. For example, SO can be divided into stress in plants SO-P with regard to the specifics of the nonspecific response of a plant organism, insect stress, etc.

Such structuring is approached unconsciously when discussing stress at the cellular level. For example, researchers make extensive use of the term endoplasmic reticulum (ER) stress, which is a nonspecific evolutionarily conservative response of cells to various influences that lead to their death, including adaptive mechanisms by which intracellular homeostasis can be restored [36, 37]. The use of the term reactive oxygen species (ROS) stress is also common. In various cells, this is a way of activating transcription factors for adaptation to stressors as "...ROS directly activate transcription factors for adaptation to stress" [38].

Terms such as ER stress and ROS stress may be regarded as components of cellular stress (SC-ER and SC-ROS). If necessary, cellular stress could also be subdivided into cytoplasmic stress, nuclear, and genomic stress. The use of such designations would immediately and accurately reveal its content to a specialist in a discussion.

Such an approach, the creation of structures of related terms based on the consideration of an important biological concept of stress, is a recommended method for scientific historicism, which enables the proactive development, supplement, and deepening of important scientific concepts without a loss of accuracy.

Acknowledgments

I express my deep gratitude to Dr. Nina Georgievna Lopatina, Ph.D., and the Academician of the Russian Academy of Sciences, Sergey Georgievich Inge-Vechtomov, for a comprehensive discussion of the material in this publication.

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