Our stress-resilient body

From the early, evolutionary developments to the integrative discovery of Hans Selye

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Executive Summary

The human body has numerous built-in mechanisms to withstand and resist external environmental changes and physical stressors. This is partly due to evolutionary benefits, like belonging to warm-body biological creatures and rapid mobilizations of internal factors, such altering blood pressure and making energy sources (e.g., blood glucose) easily available. The first scientist who made breakthrough discoveries along these lines was the famous French physiologist Claude Bernard in the middle of 19th century. Based on his research of physiological processes, he called attention to the 'stability of our internal environment'. This concept was further expanded in the early 20th century by the American physiologist Walter Canon who recognized the importance of rapid release of epinephrine (adrenaline) from the adrenal medulla that makes us ready to 'fight or fly' in difficult situations. By discovering the importance of catecholamines e.g., epinephrine, norepinephrine), he expanded the concepts of Claude Bernard and named these stable, predictable bodily reactions 'homeostasis'. Hans Selye (1907-1982) further expanded these findings by recognizing the "general adaptation syndrome" that we now call biologic stress response. This was not just a conceptual expansion, but major discovery, e.g., by realizing that the adrenal cortex plays a larger and long-standing role in these adaptive reactions. Namely, the glucocorticoid hormones, like cortisol (in humans) and corticosterone (in rats and mice) released from the adrenal cortex remain active in the blood/body for 2-3 hrs, as opposed to the few minutes of half-life of catecholamines. Selye also recognized that the biologic stress response in experimental animals consists of 3 stages: a short alarm reaction, followed by a longer stage of resistance, that may end up with stage of exhaustion. A few decades later, during the recent COVID-19 pandemic, the then recognized 'post-COVID stress response' also consists of 3 stages in human patients. The most recently recognized element in stress investigations is stress resilience, e.g., learning from bad experiences and bouncing back with positive energy, or as Hans Selye called in his animal experiments in the 1950s, creating "cross resistance". The cyclical pattern of stress resilience refers to the fundamental mechanism through which resilience develops and strengthens. It shows individual adaptive capacity, which will become deeper and more stable with each "wave" of experience. The ultimate goal in life should be, since "stress is the salt of life" (Selye) that cannot be avoided, to create a life with minimal distress and plenty of eustress. e.g., by learning and practicing stress resilience techniques.

Introduction

Human beings are at the top of the evolutionary tree, and by this, we have inherited numerous options and mechanisms of resistance and resilience. One of our top features is that we are warm-blooded mammals, and by this, we can tolerate a wide range of temperature extremes. This inherited evolutionary resistance was further refined by the famous 19th-century French scientist Claude Bernard (1813-1878) (Claude Bernard biography). Wikipedia also cites Bernard Cohen of Harvard calling Claude Bernard "one of the greatest of all men of science" (Claude Bernard). He was indeed so famous that when Hans Selye established his new Institute of Experimental Medicine and Surgery in 1945/46 at the University of Montreal, he created a “Claude Bernard Visiting Professorship” that eventually included many Nobel laureates and candidates.

One of the reasons Hans Selye dedicated this visiting professorship to the name of the famous French scientist is that he not only liked Bernard’s book on “An Introduction to the Study of Experimental Medicine” but also expected that all his PhD students at the institute would read this short book.

The stability of our internal environment: *Claude Barnard*

Claude Bernard was described as “founder of modern medicine”, and was the first (and one of the very few) French scientists to have been honored with a national funeral (Claude Bernard). Claude Bernard "explained that the body is 'relatively independent' of the outside world, and Bernard observed that living organisms maintain a relatively stable internal environment despite fluctuations in external conditions, describing how the body's internal systems adapt to environmental deficiencies to preserve physiological balance. This famous physiologist is also “known for his discoveries concerning the role of the pancreas in digestion, the glycogenic function of the liver, and the regulation of the blood supply by the vasomotor nerves. On a broader stage, Bernard played a role in establishing the principles of experimentation in the life sciences, advancing beyond the vitalism and indeterminism of earlier physiologists to become one of the founders of experimental medicine. His most seminal contribution was his concept of the internal environment of the organism, which led to the present understanding of homeostasis” (Claude Bernard biography). This principle of internal stability became the cornerstone for Walter Cannon's later formalization of "homeostasis" in the 1920s, which described the body's ability to maintain a relative balance of set coordinated physiological responses.

Nevertheless, contemporary stress resilience research has expanded far beyond Bernard's original physiological framework and this simple "recoil back" concept encompass psychological, social, and neurobiological dimensions. Modern understanding recognizes that resilience involves not just returning to baseline after stress ("tension"), but also the capacity for adaptive growth and positive transformation through harsh conditions. Significantly, stress resilience cannot exist by chance; it is a product of strategic cultivation based on neuroplasticity (the brain's ability to reorganize and form new neural connections), cognitive flexibility (adaptive thinking patterns), robust social support networks, and epigenetic factors that influence gene expression. This evolution from Bernard's mechanical view of stability to our current dynamic, multi-system understanding reflects how stress resilience operates through network interconnected physiological mechanisms that enable individuals not merely to survive challenges, but to thrive and develop greater adaptive capacity through intentional development of these foundational elements.

The 'fight or flight' syndrome and homeostasis concepts: *Walter Cannon*

Walter Cannon (1871 – 1945) (Walter Cannon) was chairman of the Physiology Department at Harvard Medical School (Cannon at Harvard), he gained early recognition for introducing the core principle of physiology – homeostasis. His concept transformed the understanding of any living organism. Cannon introduced the term "homeostasis" which describes the body's ability to maintain a range set of internal equilibrium and coined the designation "fight-or-flight" response: the body's response to any stimulus that mobilizes physiological resources, including the sudden release of epinephrine/adrenaline from the adrenal medulla to deal with immediate difficulties.

Walter Cannon's "fight or flight" syndrome, more accurately known as the fight-or-flight response, is a physiological reaction that occurs in response to a perceived threat or stressor. This response, first described by Walter B. Cannon in the early 20th century, prepares the body to either confront the danger ("fight") or escape from it ("flight"). It involves a complex interplay of the nervous and endocrine systems, leading to various physical changes.

The key components include:

- Sympathetic Nervous System Activation: When a threat is perceived, the sympathetic nervous system is rapidly activated. This system, part of the autonomic nervous system, triggers a cascade of physiological changes.
- Adrenal Medulla Activation: The adrenal medulla, located on top of the kidneys, releases stress hormones like epinephrine (adrenaline) and norepinephrine into the bloodstream.
- Physiological Changes: These hormones and the sympathetic nervous system activation lead to a range of physical changes, including:
    - Increased heart rate and blood pressure
    - Rapid breathing
    - Dilation of pupils
    - Increased blood flow to muscles
    - Release of stored energy (glucose)
    - Suppression of non-essential functions like digestion
- Purpose: The fight-or-flight response is an adaptive mechanism that helps individuals survive dangerous situations by providing them with the energy and physical capabilities needed to either fight or flee. (Cannon's fight-or-flight syndrome)

Acute response to any stimulus was also an evolutionarily adaptive response for survival, and Cannon's insights laid the basis for understanding how activation of human body systems could become maladaptive. Modern stress resilience strategies now focus on optimizing the balance between activation and recovery of these basic physiological systems, recognizing that effective resilience involves not just the ability to handle a proper stress response, but equally important, the capacity to efficiently return to homeostatic balance and prevent maladaptive changes which could create disorders or diseases, like chronic inflammation or metabolic disorders.

The biologic stress response and heterostasis: *Hans Selye*

Hans Selye (1907 – 1982) was born in Vienna to an Austrian mother, while his Hungarian father was a high-ranking surgeon in the Austro-Hungarian army. He grew up in Komarom (now Komarno in Slovakia), where his father had a private medical clinic. After finishing medical school at the German University in Prague, he moved to Johns Hopkins University in Baltimore, MD for a short postdoctoral fellowship, and did most of his seminal research on biologic stress at McGill University and University of Montreal. He died in Montreal shortly after he retired from active research and teaching.

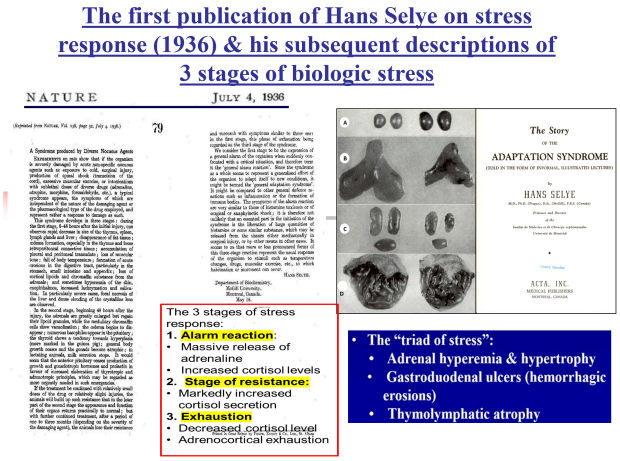
Selye was younger than Cannon and their scientific research work partially overlapped. Consequently, Selye always gave much recognition, both in his publications and lectures, to Cannon's 'fight or flight' syndrome. However, he also often complained privately (Szabo-Selye, personal communications) that the Harvard physiologist did not return this courtesy to him... Selye was not only generous in recognition toward Cannon, but he expanded the concept of homeostasis by adding "heterostasis" in the last two decades of his stress research. Namely, although Selye's seminal papers on the discovery of 'nonspecific adaptation response' and the critical role of the adrenal cortex were published in 1936 and 1937, his continued investigations of steroids led him to the recognition of catatoxic and syntoxic steroids in the 1960s and 1970s. Catatoxic steroids (Selye, 1969), e.g., most androgens and some synthetic steroids like pregnenolone-16α-carbonitrile (PCN) decrease the toxicity of many chemicals by accelerating their metabolic degradation via induction of the cytochrome P-450 enzyme system in the liver (Szabo, 1979). Syntoxic steroids, such as the anti-inflammatory glucocorticoids, enable us to coexist in 'symbiosis' with many microbes by optimizing or modulating the inflammatory barrier around bacteria. For these altered states in our body, Selye created the word 'heterostasis'.

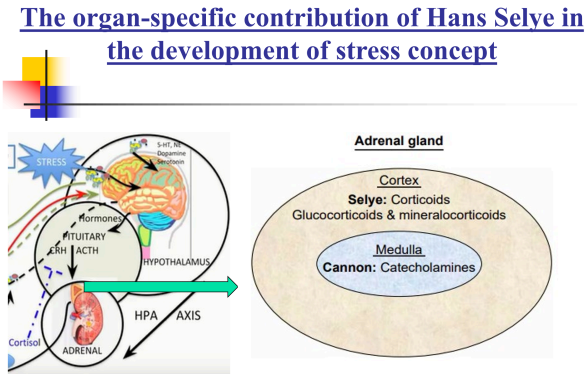
Selye's heterostasis may sound similar to McEwen's allostasis, but conceptually and mechanistically they are very different. "McEwen's allostasis refers to the concept of allostasis, which is the process by which the body adapts to stressors, leading to a state of stability through change. This involves the activation of various neural, neuroendocrine, and immune mechanisms to maintain homeostasis. However, prolonged activation of these systems can lead to allostatic load, which may result in disease over time." (McEwen, 1998). His allostasis is more akin to a philosophical, conceptual statement, whereas Selye's heterostasis is mechanistically defined by invoking specific molecular markers, natural and synthetic steroids.

The distinction between 'response' and 'mechanistic reaction' was a hallmark of Selye's early stress research, partly because he often used 'stress response' and 'stress reaction' interchangeably. This confusion is part of the reason that, despite receiving about 16 Nobel Prize nominations, he never got one, since most of the nominations emphasized his 'stress concept'. The nominations should have emphasized that he defined the mechanism of stress reaction based on key organs involved (e.g., adrenal cortex, pituitary gland) (Selye; Science, 1937; Stress in Health and Disease book, 1976) and molecules involved (i.e., glucocorticoid steroids) – not to mention that he introduced the first modern classification of steroid hormones based on their organs of origin and their mechanism of biochemical/physiologic actions (Selye, 1942, 1943). Most physicians and biochemical investigators are unaware that Selye coined the names of these steroids, such as the anti-inflammatory glucocorticoids and pro-inflammatory mineralocorticoids (Szabo et al. 2012).

The confusion about stress response vs. stress theory was not the only issue Selye suffered from... Namely, he was initially criticized for describing the stress reaction 'only' in experimental animals, mostly in rats. However, Selye described in his first and subsequent popular books (Selye, 1952, 1956, 1974), especially in his memoirs (Selye, 1979), that he got the impression and idea of 'nonspecific response' after observing and working with very sick patients as a young physician intern at the German University hospitals in Prague. To him, all these patients, regardless of the etiology of their disease, appeared uniformly lethargic, sad, depressed, often with fever, weak, without much energy... Then, fast forward to his animal experiments at McGill University in Montreal in the early 1930s, where he was trying to isolate a potential new hormone. These studies did not reveal any new hormone. However, they led Selye to recognize that these rats, irrespective of the purity of the tissue extracts, all looked sick, lethargic. At autopsy, they showed enlarged adrenal glands, shrinkage of the thymus and lymph nodes as well as gastric erosions and ulcers. This morphologic triad formed the basis of his first description of the 'nonspecific response' in his seminal publications in Nature (1936) and Science (1937).

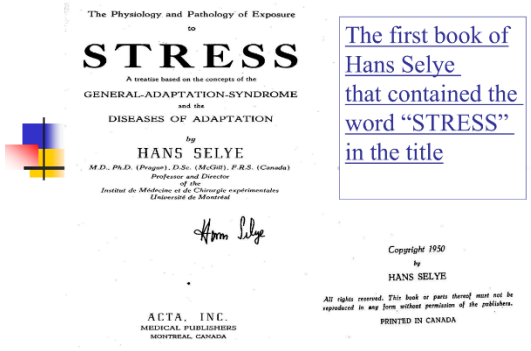
Fig. 1 (left) also shows the morphologic triad of stress response and the 3 stages of functional response to stressors. Fig. 2 (right) illustrates organ-specific contribution of Selye vs. Cannon in the physiology of biologic stress.



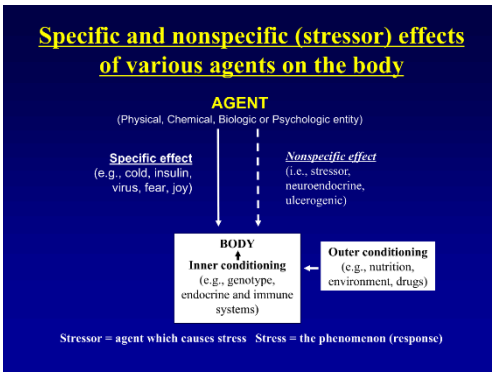


Another 'fast forward' about the human relevance of the three stages of stress response are the three stages of the so-called COVID-related stress syndrome that will be described in a special section, below.

Distress vs. eustress: Hans Selye was incredibly talented at creating novel words and new concepts or borrowing names from other branches of sciences. The first stress-related example, after naming and classifying steroid hormones (Selye, 1942, 1943), was the word stress that he reluctantly borrowed from physical science and engineering to replace the 3-word GAS (general adaptation syndrome) that he used for almost two decades. Namely, "Stress" was the title of his major (almost 1000 pages) monograph on this topic, published in 1950 in Montreal (Selye, 1950) (Fig. 3).



The first book of Hans Selye that contained the word "STRESS" in the title



After criticism that he used 'stress' both for the biologic response and for the agents that cause stress, he created the word 'stressors' for the etiologic factors. As a part of these refinements, he produced a new illustration that I adapted from his original slide to demonstrate the specific actions of biologic, chemical, and physical agents, vs. their nonspecific, stressor effects (Fig. 4 - right).

One of the last refinements of stress-related terms was the creation of 'eustress' (from euphoria and stress), after the Swedish social scientist Lenard Levi introduced the terms of 'positive stress' and 'negative stress'. Namely, Levi recognized after his studies with Swedish soldiers that not only the distress of war-simulating military exercises elevated cortisol secretion (the key hormone in stress reactions) and VMA (vanilmandelic acid – the final metabolite of catecholamine epinephrine/adrenaline) excretion in the urine, but the same metabolic changes were detected in joyful situations (e.g., watching pornographic films). Although Selye had great respect for Levi, he did not like the two-word expressions of positive stress and negative stress. Instead, he introduced in his last popular book "Stress without Distress" (1974) eustress for positive stress and retained the old English word distress for negative stress. In that book and his subsequent autobiographies he promoted the idea of creating more eustress than distress in our lives, repeatedly emphasizing what he was teaching from the early years of his stress investigations, i.e., 'stress is the salt of life', and 'life without stress is death' - implying 'distress' in these expressions.

Subsequent mechanistic studies revealed the simple physiological basis of distress vs. eustress: irrespective of the quality of cause of stressors, following the resultant increased secretion of ACTH, the cortex of the adrenal gland responds with the same increased secretion of cortisol in humans and corticosterone in rodents. Thus, although our adrenal cortex cannot distinguish between negative or positive stressors, our three brain areas can, i.e., the prefrontal cortex, the amygdala, and the

hippocampus. Furthermore, the apparent molecular marker of distress vs. eustress is the differential levels of BDNF (BDNF in distress vs. eustress).

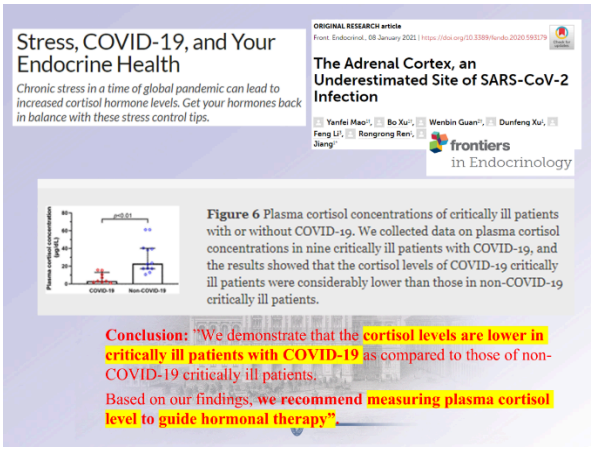
Post-COVID stress syndrome: As mentioned earlier, there were numerous scientific discussions in the early stages of stress investigations regarding whether the three stages of biologic stress response exist in humans as well, not only in experimental animals, as Selye first described. The new human confirmation came from COVID-19 clinical studies.

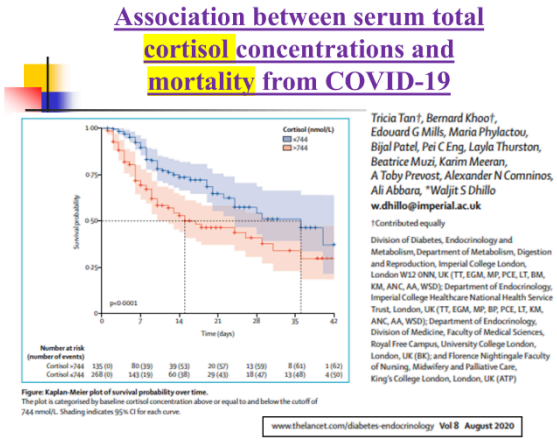
Namely, the sudden appearance of COVID-19 at the end of 2019 and early 2020 was a big surprise not only to clinicians but also to public health officials and services in most countries of the world. Based on these, often chaotic, reactions we wrote a review article in mid-2020 on “New disease and chaos with panic, associated with stress” (Szabo, 2020). However, we could not have predicted that severe COVID-19, with clinical manifestations and molecular mechanisms would so closely resemble the 3-stage stress response that Hans Selye described, based on his animal experiments more than 90 years earlier (Selye, 1936; 1937; 1976). Furthermore, as more clinical descriptions of COVID-19 started to appear in the literature, and the 'long COVID syndrome’ manifestations have been documented (Szabo, 2023), it became clear that COVID-19 is the most significant new human stressor in the 21st century (Szabo and Zourna, 2020). The subsequent clinical studies demonstrated the neuroendocrine mechanisms of what is now named ‘post-COVID stress syndrome’ that strongly resembles the first description of stress response in animals.

Interestingly, some of the early publications refer to this as a “disorder”. In contrast, others use the term “syndrome,” which is probably more appropriate since ‘disorder’ has negative connotations, as something bad. In contrast, ‘syndrome’ is a more encompassing description of changes happening in severe or prolonged cases of COVID-19. Furthermore, the adrenal changes, including the elevation of glucocorticoids, are defensive reactions, primarily due to the anti-inflammatory effects of this group of natural steroids. Some clinicians knew this much before the recognition of post-COVID stress syndrome when they started to see the beneficial effects of synthetic glucocorticoids such as dexamethasone given to hospitalized COVID-19 patients (Johnson and Vinetz, 2020; The RECOVERY Collaborative Group, 2021). One of the early editorials very correctly emphasized that “timing is everything” (Johnson and Vinetz, 2020) in controlling lung edema and inflammation, since this very potent synthetic steroid

may help before the pathologic pulmonary changes become uncontrollable by the naturally elevated cortisol.

Eventually, the initial descriptive studies on COVID-associated stress became more analytic and mechanistically oriented, and well-documented clinical studies started to show that the initial phases of severe COVID-19 hospitalized patients had elevated cortisol levels (Fig.4): this was confirmed by an extensive, recent meta-analysis (Amiri-Dashatan et al., 2022). However, as predicted by Hans Selye's animal experiments, the adrenal cortex has a limited capacity, which begins to show decline in very severe cases of hospitalized COVID-19, particularly those in the ICU. One of the most convincing case reports (Mao et al., 2021) demonstrates that even in otherwise comparable patients, SARC-CoV-2-infected patients had lower levels of cortisol than other severely ill patients (Fig. 5), left.





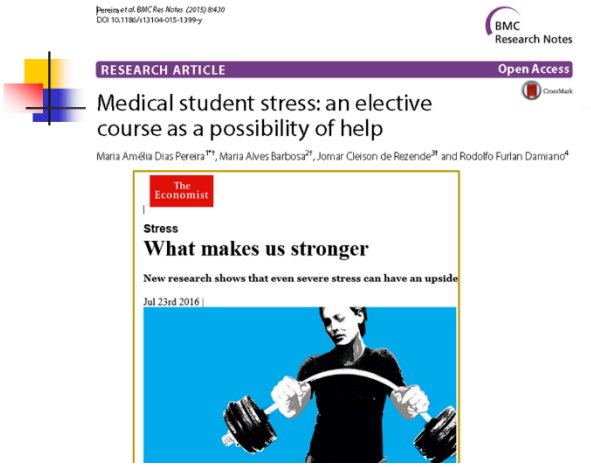
This report concluded that "the cortisol levels are lower in critically ill patients with COVID-19 as compared to those of non-COVID-19 critically ill patients. Based on our findings, we recommend measuring plasma cortisol level to guide hormonal therapy. Furthermore, not surprisingly, these authors also called attention to the fact that the adrenal cortex is "an underestimated site of SARS-CoV-2 infection" (Mao et al., 2021).

One of the most convincing clinical evidence of the 3-stages of biologic stress response in people comes from the Kaplan-Meier plots of survival probability depending on the blood concentration of cortisol in COVID-19 patients: those who had high cortisol (i.e., remained in the 'stage of resistance' with well-functioning adrenal cortex) had statistically significant better survival rates than patients with low levels of cortisol (i.e., were in the 'stage of exhaustion' of the adrenal glands) (Fig. 6) (Tan et al., 2020). Needless to say, clinicians who were aware of the potent anti-inflammatory action of glucocorticoids and paid attention to the functional stages of the adrenal cortex soon started to include potent synthetic glucocorticoids (e.g., dexamethasone) in the symptomatic, empirical treatment of severe COVID-19 patients (The RECOVERY Collaborative Group, 2021).

Thus, about 40 years after Selye's death, totally independent clinical studies reconfirmed what the old man's animal experiments showed 90 years earlier...

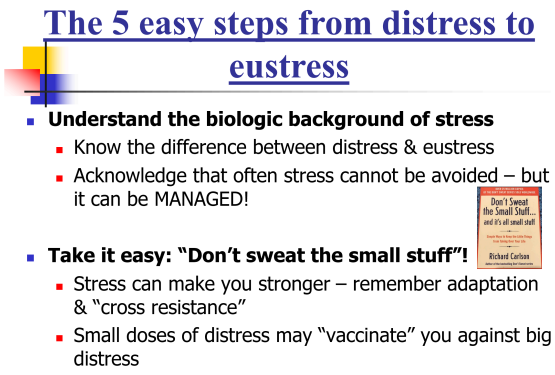
Power of resilience: How to turn on and off stress for health: Let's first briefly review if stress itself can be turned off in our life... Not, according to Selye: as we quoted him before, i.e., 'stress is the salt of life', and 'life without stress is death' - thus, no chance to completely avoid stress, i.e., distress... We then have at least three options:

a.) Better understand biologic stress response to be able to minimize the distress part and if possible, enhance eustress. A British study, also summarized in The Economist, demonstrated that students, being under the fear of distress from exams performed much better if they took a previous short course on stress (Fig. 7).



The article tellingly summarized: “Stress can make you stronger.” Selye actually discovered that small stress can make you stronger in the 1950s, and he called it “cross resistance”. Rats exposed to a small number of various stressors were subsequently exposed to a larger amount of the same stressor for a longer period and performed much better than untrained controls (Selye and Bajusz, 1961; Selye et al., 1961). This concept of cross-resistance was further developed and expanded on chemical grounds about 20 years later by Andre Robert, who obtained his PhD in Selye’s institute. After discovering “gastric cytoprotection”, he later described adaptive gastric cytoprotection (Robert et al., 1979; 1983): this refers to the prevention of acute hemorrhagic erosions in the stomach by giving rats by gavage 1 ml of 20% ethanol, 15 mins before administering 75% or 100% alcohol. The same adaptive gastroprotection can be achieved by pretreatment with dilute HCl or NaOH before giving animals concentrated solutions of acids or bases.

b.) If you cannot apply or test exposure to mild stressors to achieve resistance, then try using proven stress management techniques, like deep breathing, exercise (Robert et al., 2023) “power walk” (NY Times power walk 2025), meditation, yoga, etc. (Fig. 8, 9) These techniques can be easily applied in either 5 or 10 steps, depending on your dedication or time availability... If none of these applications help, consider seeking professional assistance or try to ride the resilience waves.



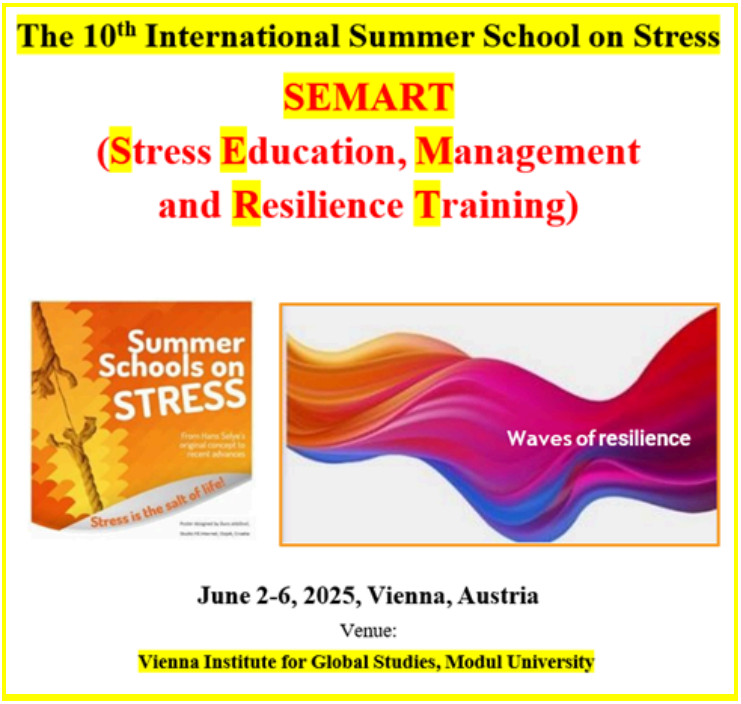
c.) Resilience is derived from the Latin word "resilire," meaning "to mechanism back" or "to recoil," which captures the essence of bouncing back from difficulty (as tension). The term "resilience" is translated as "stability, plasticity, elasticity". It is defined by the American Psychological Society (Resilience definition by APS) as:

- Successfully adapting to difficult or challenging life experiences.
- Mental, emotional, and behavioral flexibility.
- Adjustment to external and internal demands.
- Capacity to deal with change and continue to develop.
- Using shocks and disturbances to spur renewal and innovative thinking.

As we can see from the last bullet, i.e., "Using shocks and disturbances to spur renewal" or resistance is essentially the same as Selye's 'cross resistance' or Robert's 'adaptive cytoprotection'. Since this is a fluid situation, this is the reason that resilience is often perceived as waves...

The wave model of resilience: The natural rhythm of fall and rise: Resilience manifests like waves with a continuous cycle of falling and rising that creates an increasingly powerful foundation over time. Each wave cycle (challenge → recovery → growth) builds upon the previous one, and the ability to react to repeated exposure to stressors' stimuli creates what Hans Selye called "cross-resistance". This systemic human response from the whole organism resembles natural bioelectrical oscillations with elevation, peaks, and dropping to baseline, which are present in ECG, EEG, EMG, as well as in polysomnographic data. However, the crucial difference is that resilience affects experiencing setbacks (the fall), followed by recovery and growth (the rise), which refers to the network of organ interactions vs single organ activity.

We illustrated these resilience waves on the front cover of the program and abstracts of the 10th International Summer School on Stress (ISSS), hosted by VIGS (Vienna Institute for Global Studies) in Vienna, June 2-6, 2025 (Fig. 10):



This cyclical pattern is not a sign of weakness but rather the fundamental mechanism through which resilience develops and strengthens. It shows adaptive capacity, which will become deeper and more

stable with each "wave" of experience. Furthermore, stress resilience is not developed by chance, it's a product of strategic cultivation of body's transformations based on neurohormonal changes, as defined by Selye concerning the critical role of the adrenal gland (Selye, 1937) and further developed by his former PhD student, Roger Guillemin, with the discovery of hypothalamic releasing factors/hormones that earned him the Nobel Prize in 1977 (Tache et al. 2018). The other critical element in resilience has been neuroplasticity (the brain's ability to reorganize and form new neural connections), cognitive flexibility (adaptive thinking patterns) and involvement of emotional memory, discovered by Eric Kandel (Nobel Prize in 2000) (Lopez-Rojas J., Kandel E. - et al., 2022). We also face different frequencies of induction resilience waves and personal conditional "oscillations" based on individual needs to overcome challenges or have readiness for "worse time".

There are numerous interconnected factors from which depends "waves' of resilience. First, a personal baseline capacity for recovery systems, others are environmental challenges (like sauna or being at high altitude), and social networks (supportive positive influence of friends or opposite presence in life traumatic events), which determine the shape (pattern) of our resilience "waves". Understanding these factors allows for optimizing a personal resilience program, much like tuning an instrument to achieve the ideal frequency. In addition, resilience waves have multiply background characteristics, including gender differences in physiological variations in stress response patterns, general somatic health (Body Mass Index, BMI, visceral fat distribution, and cardiovascular fitness, brain-gut-fat axis activity), myriad biochemical (cortisol release, neurotransmitter levels, brain-derived neurotrophic factor (BDNF)) and immunological factors that represent defense mechanisms supporting resilience development. In summary, the right balance between all factors will create conditions for optimal "wave" in formation resilience and its sustainability.

Acknowledgments

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