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The legacy of Hans Selye and the origins of stress research: A retrospective 75 years after his landmark brief "Letter" to the Editor# of *Nature*

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Abstract
Hans Selye's single author short letter to *Nature* (1936, 138(3479):32) inspired a huge and still growing wave of medical research. His experiments with rats led to recognition of the "general adaptation syndrome", later renamed by Selye "stress response": the triad of enlarged adrenal glands, lymph node and thymic atrophy, and gastric erosions/ulcers. Because of the major role of glucocorticoids (named by Selye), he performed extensive structure–activity studies in the 1930s–1940s, resulting in the first rational classification of steroid hormones, e.g. corticoids, testoids/androgens, and folliculoids/estrogens. During those years, he recognized the respective anti- and pro-inflammatory actions of gluco- and mineralocorticoids in animal models, several years before demonstration of anti-rheumatic actions of cortisone and adrenocorticotrophic hormones in patients. Nevertheless, Selye did not receive a Nobel Prize, which was awarded in 1950 to the clinician Hench and the two chemists who isolated and synthesized some of the glucocorticoids. Nonetheless, Selye was internationally recognized as a world authority in endocrinology, steroid chemistry, experimental surgery, and pathology. He wrote over 1500 original and review articles, singly authored 32 books, and trained 40 PhD students, one of whom (Roger Guillemin) won a Nobel Prize for isolating the hypothalamic releasing factors/hormones. Here, we consider the main implications of his first article launching the biological stress concept and the key ideas and problems that occupied him. Selye considered "Stress in heath and disease is medically, sociologically, and philosophically the most meaningful subject for humanity that I can think of".

#In 1936 'Letters to Editor' were equivalent to 'Letters' as more recently published in *Nature* as original short scientific papers.

Keywords: *Anti-inflammatory drugs, corticosteroids, distress, eustress, Hans Selye, stress*

Introduction

We, former PhD students in the "Institute of Experimental Medicine and Surgery" founded and directed by Hans Selye at the University of Montreal, Montreal, Quebec, Canada, in 1945 feel the obligation to remind the scientific community about the importance of the short landmark "Letter" published by Hans Selye in Nature, just over 75 years ago (Selye 1936). Furthermore, it is important to point out the role of this article in triggering one of the most exhaustive "new wave" of endeavors of medical research of the 20th and 21st centuries. Hans Selye, MD, PhD, DSc, FRS (Canada) was the recipient of the highest state decoration in Canada: "Companion of the Order of Canada", but did not receive the Nobel Prize despite being nominated about 10 times, as recently released records indicate. He was also often called the "Einstein of medical research" (Figure 1), mostly because of his reliance and emphasis on

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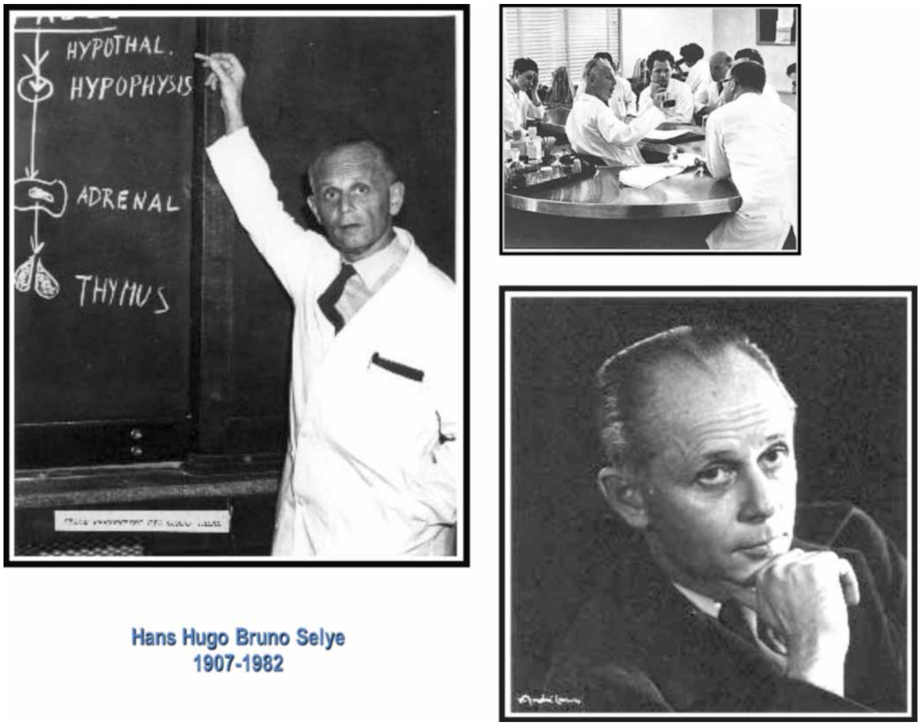

Figure 1. Photographs of Hans Selye from 1950s (left) and 1960s. (Modified from: A personal reminiscence by Dr Istvan Berczi). Selye was born January 26, 1907, Vienna, Austria and died October 16, 1982, Montreal, Canada.

creativity and originality in medical research (Selye 1975). Selye was surely an "outlier" by recent definitions (Gladwell 2008), working extremely hard and meeting the "10,000 h" rule as the most productive and creative people did in the 20th century, which is reflected by the publications of over 1500 articles and 32 single authorship books in his lifetime (Gladwell 2008). Specifically, we know from personal experiences and working with him for 4–5 years over the 30-year period of his active scientific life, that he was working at his Institute 06:00–18:00 h, 7 days/week including most traditional holidays. Thus, it is not surprising that he discovered much more than the "stress syndrome" (Table I).

Despite this huge intellectual and physical investment, he remained modest and objective, often pointing out that although he discovered the "biologic stress response," he was not the first to use the word "stress" (Selye 1950, 1956, 1976). His historic article three quarters of a century ago (Selye, July 4 1936) had the title: "A syndrome produced by diverse nocuous agents". This was a brief Letter to the Editor of Nature describing the most stereotypical manifestations of the "general alarm reaction of the organism", i.e. including thymicolymphatic involution, gastric ulcers, lipid discharge from the adrenal, and loss of chromaffinity in the medulla that Selye established as a non-specific adaptive response to various kinds of agents. The word "stress" was not used, but his first comprehensive monograph (Selye 1950) on the subject published in 1950 in Montreal had the short title "Stress" (Figure 2). This was followed by a series of "Annual Reports of Stress" published during the subsequent 5 years by the same publisher. In addition to these books and hundreds of original and review articles devoted to stress research using animal models (University of Montreal 1970; Szabo 1985), he extended his research interest to other fields. Namely, he discovered, through not ignoring "unexpected results" (Szabo 1985), calciphylaxis, anaphylactoid edema, new roles of mast cells, new models of experimental cardiovascular diseases, and the anesthetic properties of steroids that no doubt had some direct or indirect connections with the "stress syndrome" (Selye 1962, 1965, 1968, 1970; Szabo 1985). At the end of his productive research life, he returned to the field of "Hormones and Resistance" (Selye 1971) and recognized the "catatoxic" and "syntoxic" effects of steroids (Selye 1969, 1971; Selye et al. 1969) and the difference between distress and eustress (Selye 1974).

Table I. Hans Selye: major original discoveries and contributions.

- Stress syndrome (*Nature*, 1936; *Lancet*, 1943).
- Classification and naming of steroids (*Science*, 1941; *Nature*, 1943; *Endocrinology*, 1942; 1944).
- Anti-inflammatory action of glucocorticoids and pro-inflammatory action of mineralocorticoids (*Can Med Assoc J*, 1942, 1943, 1949; *Am J Physiol*, 1943; *Lancet*, 1940, 1946; *JAMA*, 1944).
- Steroid anesthesia (*Am J Physiol*, 1941; *Endocrinology*, 1942).
- Catatoxic steroids (*Science*, 1969).
- Distress versus eustress (*Book*, 1974).

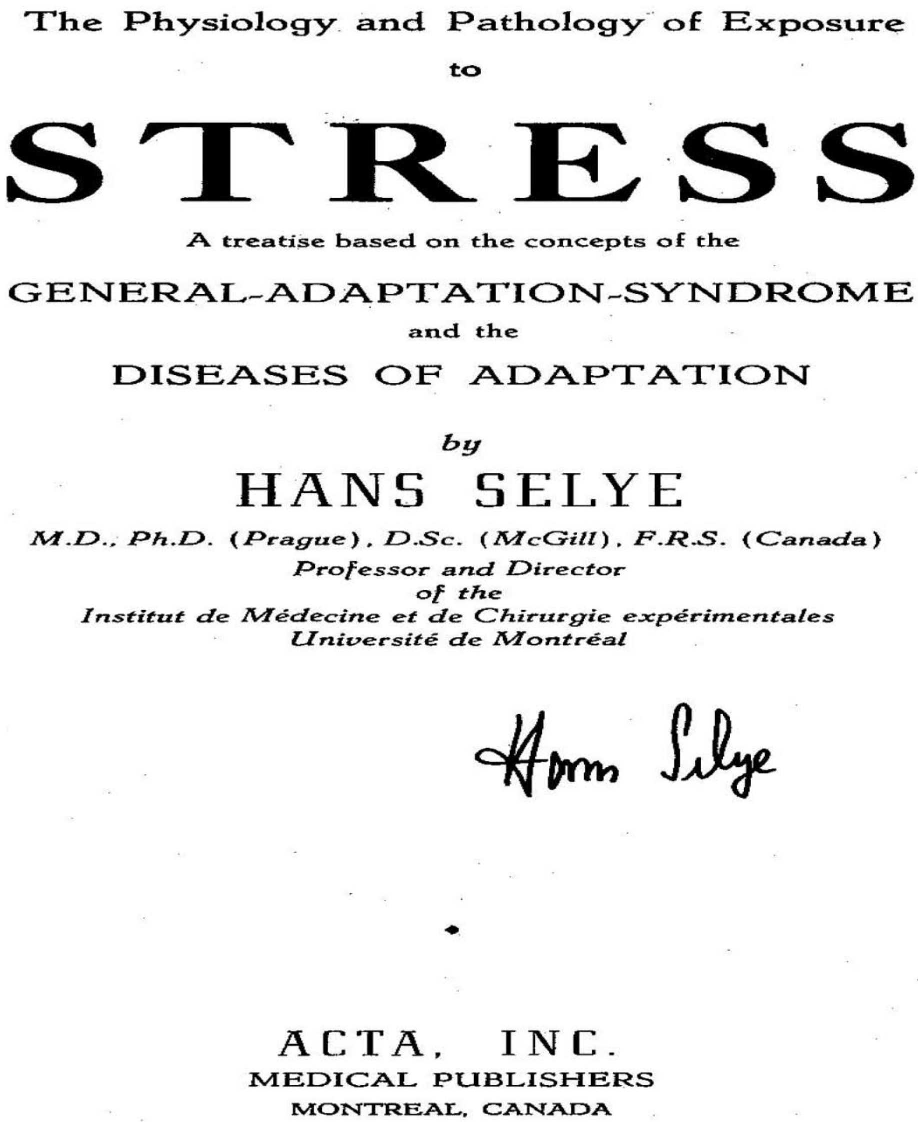
The Physiology and Pathology of Exposure
to
STRESS
A treatise based on the concepts of the
GENERAL-ADAPTATION-SYNDROME
and the
DISEASES OF ADAPTATION
by
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Figure 2. Cover page to the first monograph by Selye on stress published in 1950.

Specific versus non-specific effects

Selye's first definition of stress was "the non-specific neuroendocrine response of the body" (Selye 1936, 1956, 1976). Later on he dropped "neuroendocrine" because he realized that in addition to the involvement of the neuroendocrine system, almost every other organ system (e.g. especially the cardiovascular, pulmonary, and renal systems) is affected in one or several stages of the stress response, i.e. in the alarm reaction, stage of resistance and/or stage of exhaustion (Selye 1956, 1971, 1974). Yet, he never gave up the emphasis on non-specificity as the main characteristics of stressors, i.e. various agents that cause stress. In particular, we know from his books (Selye 1950, 1956, 1971, 1974, 1976) and our personal communications with him that he was greatly concerned by criticism in the late 1940s and early 1950s that he named both the cause and effect as "stress". Hence, being prone to create new names and definitions, he started to use the word "stressor" as the factor/agent that triggers the "stress" response. He went out of his way to emphasize that the stressor may be physical (e.g. cold and heat), chemical (e.g. formalin and ether), or psychologic in nature.

Historically, Selye's favorite example of specific versus non-specific was the stressor effects of insulin (Figure 3). He used a variant of this figure in almost all his lectures on stress, emphasizing that insulin injection decreases blood glucose levels (specific effect of this hormone), yet in large doses, especially, after repeated injections in experimental animals, it causes a stress reaction, i.e. elevates the secretion of catecholamines and corticoids, with the consequent morphological changes of the "triad of stress" (Figure 4) (Selye 1936, 1950, 1956, 1971, 1974, 1976). This involves the enlargement of the adrenal

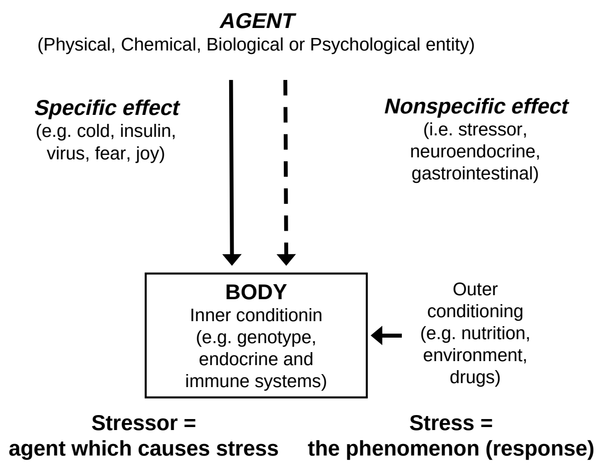

Figure 3. Illustration of the specific and non-specific (stressor) effect of various agents (modified from Szabo 1998).

glands (i.e. source of catecholamines and glucocorticoids), atrophy of the thymus, and lymph nodes (due to the now well-known effects of glucocorticoids on lymphocytes) as well as gastroduodenal erosions or ulcers (Selye 1943c, 1950, 1976) (Figure 4).

Until the end of his life, he complained that people used the term "stress" almost indiscriminately, commenting that "it was hard to get acceptance in the 1940s – now it is almost a household term" (Selye, personal communication). Importantly, he used to say that nobody should call an effect a "stress response" until the same effect is reproduced by *several* stressors different in nature, e.g. physical and chemical stressors. He was concerned that reviewers/editors of reputable scientific journals would allow the label of "cold stress" or "ether stress" without using any other stressors to ascertain whether the changes monitored reflect a specific response to a stimulus or a characteristic neuroendocrine response also induced by various stressors. Indeed, we agree with him that it would more likely be an effect of "cold" as such, or a specific action of ether, if no other stressors were investigated. Thus, in keeping with the original concept of Selye, it is important that researchers should use more than one agent/stressor before describing the response as "stress".

Catecholamines and "steroids" versus glucocorticoids

Hans Selye faced similar frustration (Selye, personal communication) by suggesting that not only catecholamines (released mostly from the adrena medulla) but also corticoids (steroids produced by adrenal cortex)

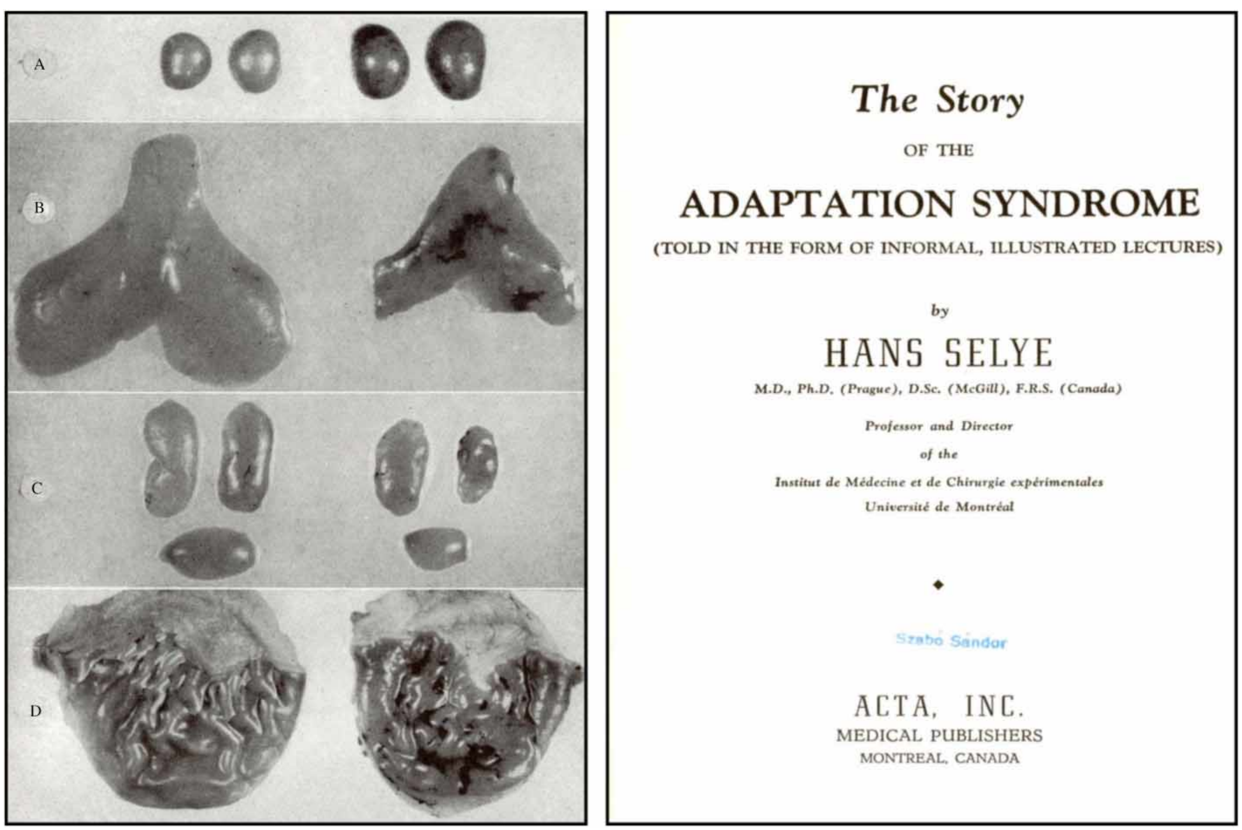

Figure 4. The typical triad of the "general alarm reaction". (A) adrenals, (B) thymus, (C) iliac lymph nodes, and (D). gastric mucosa of a normal rat (left) and one which was exposed to the frustrating mental stress of being immobilized on a metal board for 24 h. Note the marked enlargement of the adrenals (which also showed lipid discharge and hyperemia, and consequently became reddish-brown), the intense atrophy of the thymus and lymph nodes and the numerous blood-covered gastric erosions in the stressed rat (right; modified from Selye 1952).

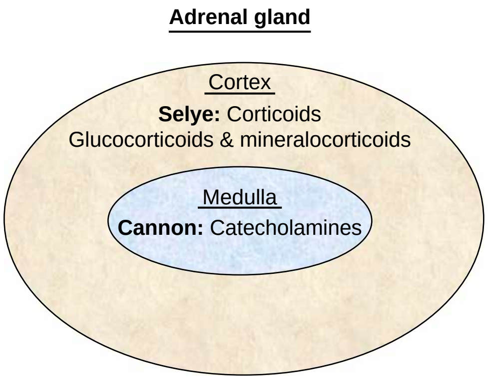

Figure 5. The organ-specific contribution of Hans Selye in the development of the biological stress concept (modified from Szabo 1998). Illustration that Selye's stress response was mostly about the adrenal cortex and the release of glucocorticoids while Cannon's emphasis was on the role played by the adrenal medulla and release of catecholamines.

Table II. The summary of Nobel lecture of Dr Hench.

PHILIP HENCH
The reversibility of certain rheumatic and non-rheumatic conditions by the use of cortisone or of the pituitary adrenocorticotropic hormone
Nobel Lecture, December 11,1950.
It may be appropriate to discuss in this Nobel Lecture three general aspects of cortisone and pituitary adrenocorticotropic hormone (ACTH): (1) the development of the theory which eventually led to the use of cortisone and ACTH in rheumatic and certain other conditions; this I shall do in some detail giving certain data not published heretofore; *(2)* the present status of cortisone and ACTH in general medicine; this topic I shall discuss summarily in view of the several current reports thereon; and (3) some major requirements for the orderly development of cortisone and ACTH as therapeutic agents; this aspect will be touched upon briefly.

under the influence of adrenocorticotrophic hormone (ACTH) and hypothalamic releasing factors/hormones (Guillemin 1978) play a role in the stress reaction. Hence, in the 1930s and 1940s the concept of Cannon's "fight or flight" syndrome (Cannon 1914), associated with the rapid and massive release of catecholamines, was widely accepted (Selye 1976; Szabo 1985, 1998). Before Selye's short article in *Nature* in 1936, the neuroendocrine response to pain or major emotions was considered to be restricted to the release of catecholamines, as proposed by Cannon (1914). Selye was the first to demonstrate the crucial role of the hypophysis–adrenal cortex axis in the stress response, and was disconcerted by the fact that while he always accepted the role of both epinephrine (adrenaline) and norepinephrine (noradrenaline) as a component of the stress response, more prominently, in the short duration of the "alarm reaction" phase, Cannon died without ever acknowledging the role of glucocorticoids that are responsible for most of the morphological manifestations of distress, especially, in the "stages of resistance and exhaustion" (Selye 1976; Szabo 1985). Because of his frustration, some of his students designed an illustration of a bisected adrenal gland that contains the names of these scientists in the appropriate parts of the gland (Szabo 1998) (Figure 5).

His biggest disappointment, nevertheless, was probably the lack of appreciation for his first modern classification and naming of steroid hormones as well as the discovery of anti-inflammatory actions of glucocorticoids (Selye 1941a, b, 1942, 1943b). He cleverly named these hormones by their sources, e.g. corticoids (originating in the adrenal cortex), testoids (from the testes), and folliculoids and luteoids (produced by the follicles and corpus luteum of the ovary, respectively). It is easy to recognize that these are the present-day corticoids, androgens, estrogens, and progestins. It should be appreciated that this classification is also based on the chemical structure of the steroids, containing 21, 19, or 18 carbons, confronting the late accusation that Selye was mainly a phenomenologist, yet he often pointed out that his PhD (obtained after the MD degree in Prague) was in chemistry. This chemical and structural approach to steroids in the 1930s and 1940s actually may be interpreted as one of the first molecular, mechanistic definitions of components of the stress reaction.

The biggest and probably the longest lasting implication of his initial classification of steroids is the recognition that glucocorticoids and mineralocorticoids (also named by Selye) regulate not only carbohydrate and mineraloid/electrolyte metabolism, respectively, but they also exert anti- or pro-inflammatory effects (Selye and Dosne 1940a,b; Selye et al. 1940, 1944; Selye 1941c, 1942, 1943a, 1946a, b, 1949; Clarke and Selye 1943; Selye and Pentz 1943; Hall and Selye 1945). These pioneering findings were published in the most prestigious research and clinical journals in the early and mid-1940s. Especially noteworthy is his publication on "Relation of the adrenal cortex to arthritis" in the *Lancet* in 1946 (Selye 1946a). Despite these contributions, the 1950 Nobel Prize in Physiology or Medicine was awarded to the clinician Dr Philip Hench (and the two chemists who isolated and identified the structure of glucocorticoids) who demonstrated the "next obvious step", i.e. that cortisone and ACTH exert clinically profound anti-inflammatory effect in patients with rheumatoid arthritis (Table II). Yet, it is sad that Hench in his Nobel lecture and 23-page manuscript that contained 113 references, made no reference to the preceding work of Selye, who demonstrated 8–10 years earlier the anti- and pro-inflammatory effect of gluco- and mineralocorticoids, respectively (Table II). It seems inconceivable that Hench (working at the prominent Mayo Clinic) would not have read some of Selye's relevant experimental studies and results, published in

Nature, *Science*, *Endocrinology*, *the Journal of the American Medical Association*, *Lancet*, and *the American Journal of Physiology* between 1940 and 1949.

There is an additional frustration about glucocorticoids that we share with our teacher. This is that Selye was bewildered by the inappropriate use (mostly by clinicians, medical residents, and students) of the term "steroids" as referring to glucocorticoids, both in conversations and publications. It is difficult to believe that these educated young and old physicians would not know that "steroids" refer not only to corticoids but also to androgens, estrogens, and progestins. Moreover, use of the relatively newly invented term "corticosteroids" disregards that the original name "corticoids" already implies the steroid nature of these natural and synthetic hormones. We would like to see more vigilance and educated enforcement of not using misleading or superfluous medical terms by clinicians and authors in publications.

Distress versus eustress

It took almost four decades for Selye to recognize that not all stress reactions are equal (despite the stereotypical neuroendocrine effects), due to differences in the subject's perception and emotional reaction. As he admitted (Selye, personal communication), the clinical and social investigations of Lenard Levi (Levi 1971) in Sweden played a major role in Selye's shift of thinking. However, until the end of his life, Selye remained a basic science researcher who never moved beyond the use of animal models of stress-related disorders. Yet, as an avid and compulsive reader of medical literature, he was pleased to see that his initial, often criticized basic investigations of the 1930s–1950s were extended by others to clinical fields, and later to sociology and psychology. It was Levi who first distinguished between "positive" and "negative" stress (Levi 1971), i.e. the cerebral cortex may recognize the difference between ACTH and corticoids being released under the influence of arguments with our spouse, and release as a result of the pleasure of kissing one's girlfriend or boyfriend.

Selye, always prone to create new names and concepts, introduced the terms "distress" and "eustress" in the early 1970s to distinguish whether the stress response was initiated by negative, unpleasant stressors, or positive emotions (Selye 1974). He was so convinced that this was a major distinction and discovery relevant not only to the relatively small scientific/research community but also to the general public, that he published these new distinctions in a book. In "Stress without distress" (Selye 1974) and the subsequent autobiographic "Stress of my life" (Selye 1977), he started to emphasize that "stress is not what happens to you, but how you react to it" (Selye 1974, 1977). Eventually, later in his life he moved even further to psychological and philosophical/theological fields, getting almost obsessed with his new integration of statements from the Old and New Testaments, hence, he used to say and write that instead of "love your neighbor as yourself", we should interpret this as "earn your neighbor's love" (Selye 1974). This sounded attractive to a lay audience, but some of us tried to remind him not to follow the mistake of other famous, creative scientists who at the end of their scientific life moved away from their well-defined fields and created mixed reactions by getting involved with fields that were not their original field of expertise.

Epilogue

Hans Selye, after his landmark short article on the "general adaptation syndrome" in 1936 (Selye 1936) at the age of 29 years, which he later renamed "stress" and used for the title of his monograph in 1950 (Selye 1950), became one of the most creative scientist of the 20th century. He repeatedly, almost daily emphasized the importance of originality in medical research (Selye 1975; Selye, personal communication), especially by using "*in vivo*" methods (Selye 1967). He was disparaging about *in vitro* approaches and looked down on those who were proud of using complex, modern methods, e. g. electron microscopy in the 1960s and 1970s, although finally he agreed to purchase a transmission electron microscope that allowed one of his senior coworkers, Kalman Kovacs to suggest that one of the main mechanisms of catatoxic action of steroids is proliferation of smooth endoplasmic reticulum, with induction of microsomal enzymes in the liver (Kovacs et al. 1970). This was confirmed by subsequent biochemical studies performed in his institute (Solymoss et al. 1969; Kouronakis et al. 1973; Taché et al. 1973). Despite all these methodological and mechanistic advances in steroid research, he was still very proud of the motto at the entrance of his institute:

> "Neither the prestige of your subjects and
>
> The power of your instruments
>
> Nor the extent of your planning
>
> Can substitute for
>
> The originality of your approach and
>
> The keenness of your observation"
>
> Hans Selye

It was a natural expansion of his emphasis on *in vivo* research approaches that he very much liked the "animal models of human disease" (Selye, personal communication). Indeed, he developed chemically induced models of almost any major organ systems (Selye 1942; Selye et al. 1944; Somogyi et al. 1968; Szabo 1985) and thanks to him, we recognized the importance of new rodent models of duodenal ulcer disease (Szabo and Selye 1972; Selye and Szabo 1973; Szabo 1976; Szabo and Cho 1988). Thus, working with animal models "only", Selye is a good role model for young investigators, by his demonstrating that through creativity and hard work, basic science researchers may discover new biological phenomena, manifestations, and mechanisms of diseases.

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