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Editorial:

Hans Selye and the stress response: 80 years after his “letter” to the Editor of Nature

Hans Selye et la réponse au stress : 80 ans après sa lettre à l'Éditeur de Nature

L. Rochette & C. Vergely

A comprehensive theoretical outline of the stress concept was published by Hans Selye, eighty years ago, in 1936 [1]. This was a brief Letter to the Editor of Nature describing the most stereotypical manifestations of the general alarm reaction of the organism. Selye's first definition of stress was “the non-specific neuroendocrine response of the body”. Before Selye's article in Nature, the neuroendocrine response to pain or major emotions was considered to be restricted to the release of catecholamines. Selye reviewed the biochemistry and pathological anatomy of adaptative responses with interpretations of the syndrome including the central functions of hormones.

Born in Austria in 1907, Hans Selye was brought up in Komárom, on the border between Czechoslovakia and Hungary. His father was a physician, as were his grandfather and great-grandfather. He received his medical degree from the German University of Prague in 1929 and two years later his doctorate in organic chemistry. Before this period, he studied in Paris (1925, visit Marie Curie Laboratory), and Rome in 1926. In 1931, he came Johns Hopkins University in Baltimore and then integrated in the Department of Biochemistry at

McGill University in Montreal In 1945, he transferred to the Université de Montréal, where he founded and became Director of the Institute of Experimental Medicine and Surgery. He held this position until his retirement in 1977. In 1979, Selye founded the International Institute of Stress and the Hans Selye Foundation. Many of his 40 books and over 1700 publications became bestsellers all over the world. Hans Selye died in 1982 in Montreal. He has been made a Companion of the Order of Canada (the highest decoration awarded by his country). He died on 16 October 1982 in Montreal ; he was named “the Einstein of medicine”.

It has been reported that the stress syndrome was discovered accidentally by Hans Selye while searching for new hormones in the placenta; is it an example of serendipity [2]? The word “stress” was not used and his first specific monography on the subject was published in 1950 with a short title: “Stress” with a subtitle: General-Adaptation-Syndrome (GAS) and the diseases of adaptation. In this article he terms the response to stress as the GAS, which is demonstrated by experimental facts. He also predicts that diseases of adaptation do exist. One of his greatest contributions was the demonstration of the stress triad (gastrointestinal ulceration, thymico-lymphatic atrophy and adrenal hypertrophy) and of the role of the hypothalamus in stimulating the hypophysis, that in turn, induced the adrenals to produce corticoids. The discovery of the steroids: adrenocorticotrophic hormone (ACTH), Growth releasing hormone (GRH), somatostatin and other hypothalamic and pituitary releasing factors and hormones was initiated by these initial and major physiological concepts. During the late 1930s and 1940s Hans Selye explored the physiological stages of the adaptation syndrome and clarified the central role of the adrenal glands in adaptive reactions. The adaptative response of each individual to stress is

determined by a multiplicity of genetic, physiological and environmental factors.

Hans Selye extended his research interest to original animal models and he focused a part of his research on steroid hormones originating from the adrenal cortex that play a crucial role in stress response. He discovered in animal models the pro-inflammatory effect of mineralocorticoids and the anti-inflammatory properties of glucocorticoids. In 1949, Selye discovered that inflammatory responses induced by a compound such as croton oil in rats is inhibited by cortisone or by purified ACTH and showed that a mineralocorticoid: deoxycorticosterone acetate aggravates the process. The process of inflammation and “diseases of adaptation” were developed by Selye in his book “Stress in Health and Disease” [3].

He suggested that not only catecholamines released from the adrenal medulla and adrenergic neurons but also corticoids, steroids produced by adrenal cortex under the influence of ACTH and hypothalamic releasing factors/hormones played an important role in the stress reaction. The existence of a "first mediator" in the hypothalamus able to orchestrate the adaptation in the body had been demonstrated [4, 5]. This factor that elicited ACTH release from the rat pituitary was named it corticotropin releasing factor (CRF). In 1981, CRF was characterized CRF as 41 amino acid and cloned the CRF1 and CRF2 receptors [6].

Selye used the word “stressor”. The stressors could be psychological (fear, anxiety, etc.) or physical (cold, heat, pain, etc.) or such that have both psychological and physical components, inducing diseases; the changes of the body reflecting numerous responses induced by stressors. It has now become accepted that the immune system and

neuroendocrine system form an integrated part of our physiology [7, 8]. The central role of both endocrine regulation and of the regulation of the immune system by the central nervous system is well known in the process. The environmental stressors and emotional influences can play a role in the development of various diseases (e.g. cardiovascular...)

The effects of chronic stress are being investigated in a number of domains-including cardiovascular diseases. Depressive state is prevalent in coronary heart disease (CHD) patients and increases risk for acute coronary syndrome (ACS) recurrence and mortality despite optimal medical care. Research has shown that psychological stress can trigger ACS and sudden cardiac death. The pathways underlying this risk remain non elucidated [9].

Hans Selye demonstrated the essential role of the hypophysis–adrenal cortex axis in the stress response, associated with the “alarm reaction” phase: the stress adrenergic response. He showed that rats develop similar hypertrophy of the adrenals, involution of lymphatic organs and gastric erosions in response to exposure to harmful agents independently of their chemical or physical nature. As we reported CRF was one of the first hypothalamic releasing factors to be named and characterized. Convincing evidence established that CRF receptors mediates the peripheral effects of the CRF signaling system on the heart and blood vessels; CRF2 being densely expressed in the cardiovascular system [10]. In contrast to short-term stressors, chronic stress has been shown to suppress or dysregulate immune function [11]. In 1970, Selye introduced new terms such as “distress” and “eustress” distinguishing the characteristic of the initial stress: negative, unpleasant **stressors**, or positive emotions.

Hans Selye has also a historic role in the classification of steroids. He had a focused research on steroid hormones originating from the adrenal cortex that play a crucial role in stress response. He performed the chemical and structural approach to steroids in the 1930s and 1940s. The classification is based on three facts: 1) the names of steroid groups are identical with their organ of origin (e.g., corticoids from the adrenal cortex, androgens from the testis); 2) chemical structures of the steroids are identical within a group (e.g., steroids containing 18, 19 or 21 carbons); and 3) the biological effects are homogenous within a group [12]. Selye was also one of the firsts to demonstrate that stress is associated with induction or exacerbation of ulcers in the stomach; and duodenum. Stressors in rodents affect mostly the stomach and cause only gastric erosions ("stress ulcers"). In 1970s it is demonstrated that compounds such as propionitrile or cysteamine selectively induced duodenal ulcer in the rat [13].

Now, with the development of biochemistry and cellular fields, biological formulations of stress appeared; extending the initial stress concept established by Hans Selye. There are few data available at present that implicate the different stress (psychological, cellular: oxidative, mitochondrial, reticular...) in physiological and detrimental process. Eighty years later, more than 685,000 published articles discuss the contributions of the stress in PubMed data. Numerous applications have been proposed for the concept of stress, each focusing on aspects of an internal or external challenge, on stimulus perception by an organism; or on a physiological and cellular response to the stressors Both mitochondria and the endoplasmic reticulum (ER) are suitable of adaptive responses. Mitochondrial stress and ER stress are central to the maintenance of cellular

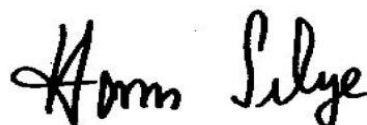
homeostasis. Indeed, an evidence of considerable cross-talk between the two organelles exists. Now there is increasing recognition of an interaction between the functions of mitochondria and ER with oxidative metabolism validated via oxidative stress [14, 15]. Concerning the whole aspects of oxidative stress, the cumulative number of papers published exceeds 158,000 since 1980. The term began to appear in the 1970s, coincident with superoxide and superoxide dismutase discovers [16].

In conclusion, now, the concept of stress is extended to biological parameters. Physiological homeostasis is a dynamic equilibrium of the body maintained by the interplay of various biological process associated to the live. "Stress is the spice of life," both good and harmful stress, use up the body's adaptive energy" said Hans Selye. Hans Selye was nominated for the Nobel Prize in Physiology and Medicine seventeen times between 1949 and 1953, particularly for his "work on endocrinology and the adaptation syndrome," for his contributions to the "isolation of steroid hormones," and for his formulation of "stress reactions." Selye's theories of adaptation and stress were not unequivocally accepted by his contemporaries.

"In the end," Hans Selye said in an interview, "I doubt whether modern man experiences more distress than his ancestors. It's not that people suffer more stress today. It's just that they think they do."

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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Déclaration des liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

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