Inflammation Research (2019) 68:177–180
https://doi.org/10.1007/s00011-018-1199-7

Inflammation Research

HISTORY OF INFLAMMATION

Hans Selye and his studies on the role of mast cells in calciphylaxis and calcergy

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Received: 7 November 2018 / Accepted: 12 November 2018 / Published online: 19 November 2018

Abstract
Hans Selye was an endocrinologist, a pioneer of research on biological stress in human individuals and groups. His most important scientific contributions include in 1936 the evidence that the pituitary–adrenal–thymus axis was activated by various nocuous stimuli, which led to the involution of the thymus and of the lymphoid organs; in 1946, the theory of general adaptation syndrome (GAS), pointing out that this is a general reaction that leads to resistance of the organism to various insults. This review article is focused on the general interest of Selye on the important role played by mast cells in different pathological conditions and in particular in calciphylaxis and calcergy, summarized in a classic book, which is a lasting contribution on the subject.

Keywords Calciphylaxis · Calcergy · General adaptation syndrome · History of medicine · Mast cells · Stress

Biographic sketch

Hans Selye (Selye János in Hungarian), was born in Komarno, Slovakia (at that time Komárom, Hungary) on January 27, 1907. Selye attended school at a Benedictine monastery, and since his family had produced four generations of physicians, entered the German Medical School in Prague at the age of 17. He continued his medical education at the University of Paris, transferring in 1926 to the University of Rome. He then returned to Prague to take his medical degree and a doctorate in chemistry in 1931. That same year he came to the United States as a Rockefeller research fellow at "Johns Hopkins University" in Baltimore. Dr. Selye completed his Ph. D and migrated at Mc Gill University, where he became a lecturer in biochemistry in 1932. In 1945, he joined the University of Montreal and founded the "Institute for Experimental Medicine and Surgery" and remained there until 1976 (Fig. 1). In 1979, he founded the "Canadian Institute of Stress", and continued to working until his death, on October, 16, 1982. Dr. Selye is survived by his wife, Louise (Fig. 2), and five children: Catherine, Michel, Jean, Marie and Andre.

Dr. Selye wrote more than 1700 scholarly papers and 39 books on the subject. At the time of his death on October 16,1982, his work had been cited in more than 362,000 scientific papers, and in countless popular magazine stories, in most major languages and in all countries worldwide. He is still by far the world's most frequently cited author on stress topics. Two of his eighteen books, "The Stress of Life" and "Stress Without Distress" were unequaled bestsellers (the latter in 17 languages). In addition to his three earned doctorates, Dr. Selye has received sixteen honorary degrees from various universities in the United States, Canada, South America, and Asia. He 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 ten times.

The discovery of the "General Adaption Syndrome"

In 1936, at the age of 29 years, Selye published his first paper in form of a brief letter to the Editor of "Nature" in which he described thymic-lymphatic involution, lipid discharge from the adrenal, loss of chromaffinity in the

Responsible Editor: John Di Battista.

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Fig. 1 A portrait of Hans Selye

Fig. 2 A portrait of Hans Selye and his wife Louise

medulla and the formation of acute erosions in the digestive tract, particularly in the stomach, small intestine, and appendix of the animals (rats) following exposure to noxious agents. He named this syndrome as "General Adaptation Syndrome" (GAS) as a non-specific adaptive response to various kinds of agents [1].

There are three stages in the process, he said: alarm reaction, resistance and exhaustion. In the first stage, the body acknowledges the cause of the stress, which could be, say, the news of a raise or losing a job. The body's response is immediate. The pituitary–adrenal–cortical system produces the hormones necessary for either ''flight'' or ''fight,'' that is, either adapting to the stress causing the situation or resisting it. He pointed out that this is a general reaction that leads to resistance of the organism to various insults. Selye noted that regardless of the type of shock the rats were exposed to, a similar set of symptoms could be observed shortly afterwards, indicating that the reaction was not to a specific stimulus but part of a more general reaction to stressful situations.

Ten years later, Selye published a full account of his experimental findings [2] and in 1950, he published a comprehensive monograph, in which for the first time the term "stress" was used, to define the physiological adaptive responses of the organism to emotional or physical threats ("stressors") [3]. In 1949, Selye discovered that the inflammatory response is regulated by corticosteroids [4]. In his article entitled "Stress and Disease", he proposed that deficient host defense due to abnormalities of neuroendocrine factors may lead to disease [5]. Selye extended the theory to humans, demonstrating that a stress-induced breakdown of the hormonal system could lead to conditions, such as heart disease or high blood pressure that he called "disease of adaptation".

Selye has acknowledged the influence of Claude Bernard (who developed the idea of milieu intérieur) [6] and Walter Cannon's "homeostasis" [7]. Selye discovered and documented that stress differs from other physical responses in that stress is stressful whether one receives good or bad news, whether the impulse is positive or negative. He called negative stress "distress" and positive stress "eustress" [8, 9]. The system whereby the body copes with stress, the hypothalamic–pituitary–adrenal axis (HPA axis) system, was also first described by Selye. He also pointed to an "alarm state", a "resistance state", and an "exhaustion state", largely referring to glandular states. Later, he developed the idea of two "reservoirs" of stress resistance, or alternatively stress energy [8, 9].

The interest of Selye in the study of mast cells

In 1965, Selye published a monograph entitled "The mast cells" (Fig. 3) in which the author provided a detailed survey of the existing data on mast cells containing more than 2500 references published since the discovery of mast cells and organized it into ten chapters: "history, definition and terminology, histology, embryology, comparative anatomy, agents

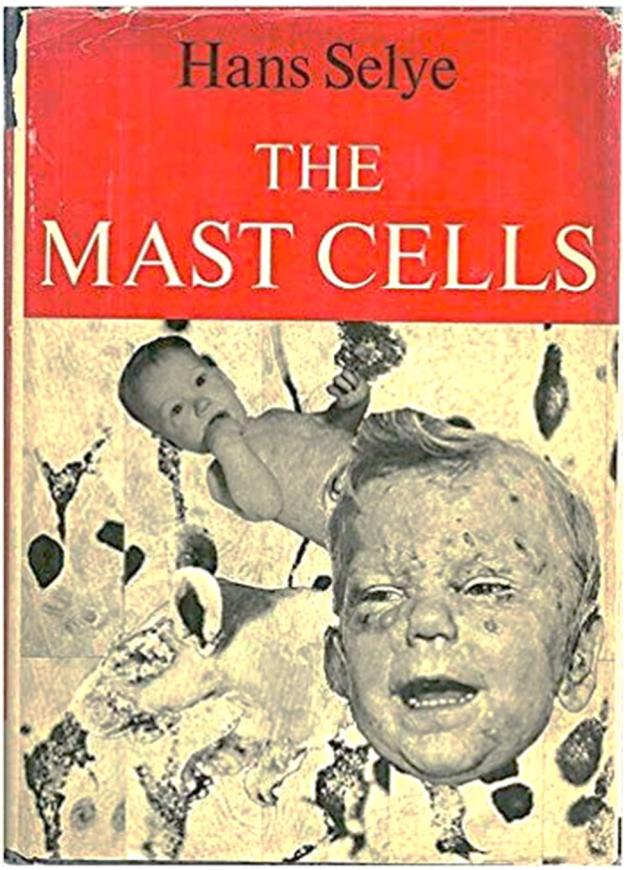

Fig. 3 The cover of the monograph entitled "The Mast cells"

affecting mast cells, diseases, biochemistry, the basophils and theories [10]".

In the Foreword of this book, Selye wrote that: "My own interest in the mast cell was first aroused by the discovery of the anaphylactoid reaction, the peculiar Quincke edema-like, acute swelling and hyperemia of the snout, paws, and genital region elicited by the parenteral administration of egg white in the rat. (…) The only obvious common feature of all these "anaphylactoidogenic" agents is that they cause acute mast cell degranulation in the target areas in which they elicit edema and hyperthermia. Conjointly with the discharge of the metachromatic granules, histamine and 5-HT are released from the cytoplasm and the anaphylactoid response can be prevented by antagonists of histamine and 5-HT, as well as by a previously induced mast cell-discharge. All these observations suggested that mast cells and their specific products are intimately related to the pathogenesis of these "anaphylactoid reactions" (pages VIII–IX).

The role of mast cells in calciphylaxis and calcergy

In the years 1960–1962, Selye has discovered a new biological phenomenon, named calciphylaxis [11]. Calciphylaxis is a serious, uncommon disease in which calcium accumulates in small blood vessels of the fat and skin tissues, and causes blood clots, painful skin ulcers and cause serious infections that can lead to death. People who have calciphylaxis usually have kidney failure and are on dialysis or have had a kidney transplant. The condition can also occur in people without kidney disease [11].

Calcergy is a phenomenon which resembles calciphylaxis but differs from the latter in that no sensitization with a calcifying compound is needed to elicit it [12, 13]. It is another experimentally induced model of pathologic calcification, a form of soft-tissue calcification which occurs wherever direct calcifiers or 'calcergens' come in contact with connective tissue. Calciphylaxis is somewhat different from a generalized anaphylactic reaction but there are some key points that point towards an allergic reaction [12]. What Selye describes here is a sensitization assay with dihydrotachysterol (DHT, a synthetic vitamin D analogue) and multiple injections of egg white (a strong allergen) in rats. Treated animals developed "a massive cutaneous calcification" with painful skin; Selye's calciphylaxis research was a part of a rising trend of research on human senescence [11].

Mast cells are involved in these processes. As Selye wrote in the Foreword of his book on mast cells: "It was noted that certain types of calciphylaxis and calcegry can be elicited in suitably sensitized animals by treatment with histamine liberators. When the latter cause a sudden mast cell discharge under these conditions, the metachromatic granules undergo calcification as soon as they emerge from the cell body. It has long been known that certain metachromatic polysaccharides appear both in organic bone matrix and in extraskeletal tissues undergoing calcification. Studies on the histogenesis of calciphylactic and calcergic lesions suggested that the metachromatic mast cell material may act as a calcium trap. Furthermore, histamine- and serotonin-blocking agents (e.g., cyproheptadine), as well as a pretreatment with a mast cell-discharger before sensitization, actually prevent those same forms of calciphylaxis and calcergy that are normally elicited by treatment with mast cell-dischargers after sensitization. All these findings suggested that mast cell may have yet another hitherto unsuspected function, namely, that of providing a matrix for the binding of calcium salts and the metals used for the production of calciphylaxis and calcergy" (page IX).

Selye [14] interpreted mastocalciphylaxis as a phenomenon in which mast cell degranulation, induced following

suitable sensitization, causes the attraction of various blood-borne metals to discharged mast cell granules. Selye [14] and Gabbiani et al. [15] demonstrated that in calciphylactically sensitized rat, treatment with polymyxin results in the precipitation of calcific material around cutaneous mast cell granules. If calciphylactically sensitized rats are treated with iron preparations in which the metal is combined with a mast cell discharger that produces a typical anaphylactoid inflammation, the anaphylactoid shock organs became heavily calcified. Selye [14] demonstrated that in rats calciphylactically sensitized with DHT which induced directly the mobilization of calcium not through the stimulation of parathyroid hormone, thorium–dextran i.v. produces mast cell degranulation and calcification predominantly around the shoulder and hip joints.

Selye et al. [16] demonstrated that in rats calciphylactically sensitized with DHT, aluminum dextran, a mast cell discharger, produces calcification in the autonomic nervous system and in anaphylactoid shock organs. These results suggest that this calcifying syndrome is, at least in part, dependent upon mast cell degranulation. Selye et al. [17] demonstrated that different agents including distilled water, mechanical trauma, formaldehyde, croton oil, or histamine liberators selectively inhibits skin calcification at the point where they are applied. The histologic structure of the skin evidence three distinct zones: an unprotected peripheral zone which is massively calcified and shows degranulated mast cells and a diffuse metachromasia in the calcified and partly necrotic connective tissue; an intermediate zone, just inside the calcified periphery, showing little or no calcification and little or no metachromatic material in the extracellular space; a central zone, without calcification or mast cells. Selye et al. [18] showed that in rats calciphylactically sensitized with parathyroid extracts, subsequent treatment with various mast cell dischargers produce calcification of different organs. Selye et al. [19] performed further experiments performed on rats, using special histochemical stains for the demonstration of metachromatic materials, lead, calcium, phosphate and carbonate, to study calcergy. They demonstrated that in simple calcergy, when lead acetate is directly injected into the subcutis, it is seen to impregnate the collagen fibers in the injection site without noteworthy participation of the mast cells. The lead-treated area secondarily attracts calcium, phosphate and possibly carbonate. In mastocalcergy, the lead acetate is injected intravenously and local calcification is produced by the simultaneous subcutaneous injection of a mast-cell discharger such as polymyxin. Here, mast cells showed degranulation without any mineralization, but this is soon followed by lead uptake on the mast-cell granules with secondary attraction of calcium, phosphate and carbonate. Finally, the discharged and calcified mast-cell granules disintegrate into a dust-like, fine precipitate which is transferred to the circumjacent collagen fibers where it initiates an intense process of mineralization.

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