# The 80 years old 'stress' after the first article of Selye: Progress & challenges

## *- 80 Evvel Selye cikke utan: Fejlodes es lehetosegek -*

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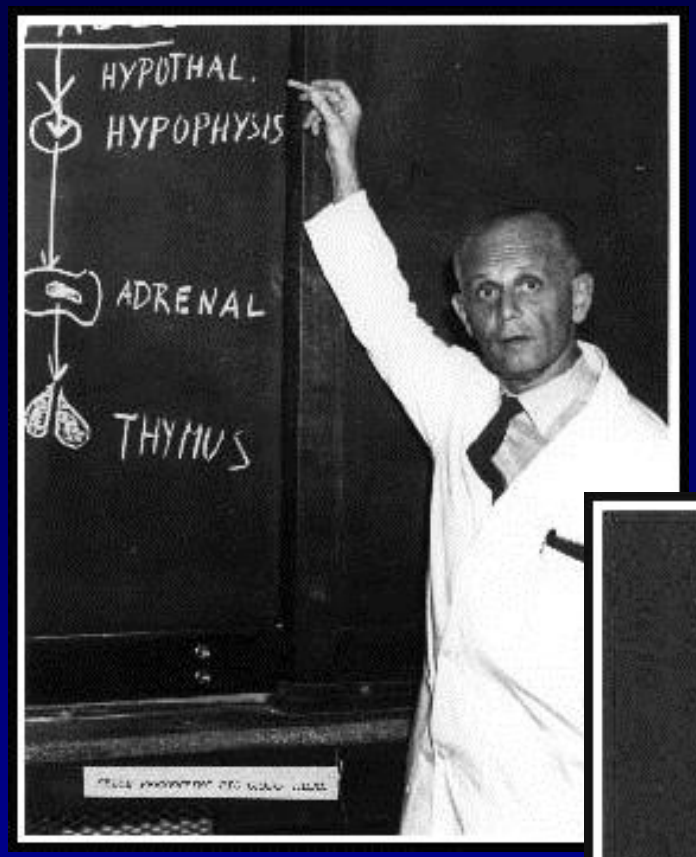
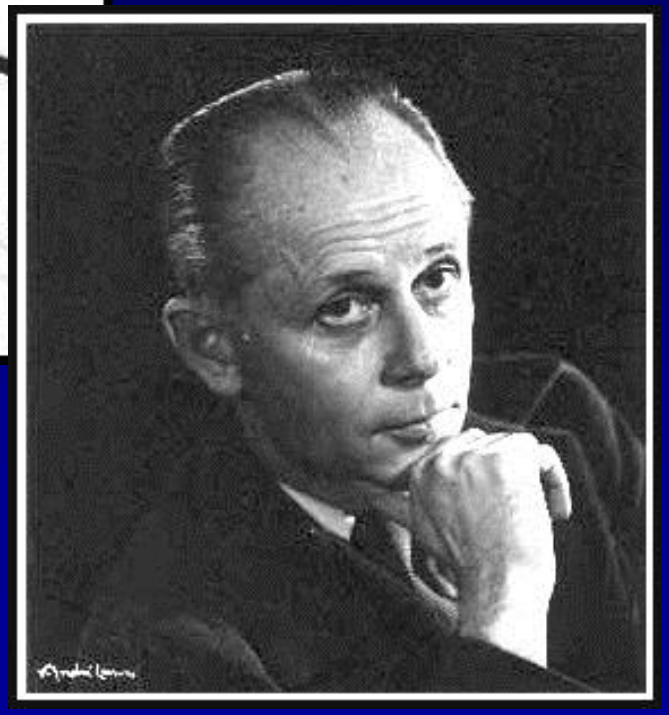
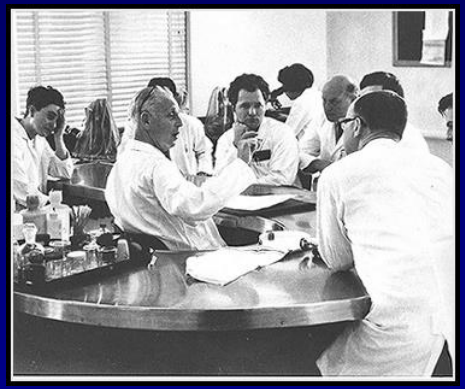



**Hans Hugo Bruno Selye**
**1907-1982**



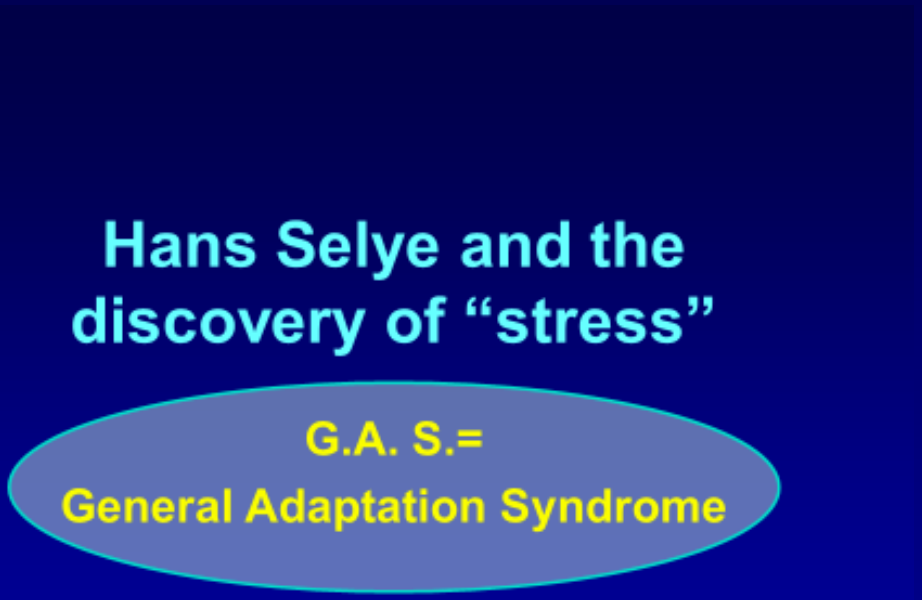


**Selye in autopsy room, University of Montreal**

- **Photos from: *A PERSONAL REMINISCENCE* by: Dr. Istvan Berczi**

# The 80 years old ‘stress’ after the first article of Selye: Progress & challenges

- History
- Progress
- Challenges



(*Reprinted from* NATURE, *Vol.* 138, *page* 32, *July* 4, 1936.)



## A Syndrome produced by Diverse Nocuous Agents

EXPERIMENTS on rats show that if the organism is severely damaged by acute non-specific nocuous agents such as exposure to cold, surgical injury, production of spinal shock (transcision of the cord), excessive muscular exercise, or intoxications with sublethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather a response to damage as such.

This syndrome develops in three stages: during the first stage, 6–48 hours after the initial injury, one observes rapid decrease in size of the thymus, spleen, lymph glands and liver; disappearance of fat tissue; œdema formation, especially in the thymus and loose retroperitoneal connective tissue; accumulation of pleural and peritoneal transudate; loss of muscular tone; fall of body temperature; formation of acute erosions in the digestive tract, particularly in the stomach, small intestine and appendix; loss of cortical lipoids and chromaffin substance from the adrenals; and sometimes hyperæmia of the skin, exophthalmos, increased lachrymation and salivation. In particularly severe cases, focal necrosis of the liver and dense clouding of the crystalline lens are observed.

In the second stage, beginning 48 hours after the injury, the adrenals are greatly enlarged but regain their lipoid granules, while the medullary chromaffin cells show vacuolization; the œdema begins to disappear; numerous basophiles appear in the pituitary; the thyroid shows a tendency towards hyperplasia (more marked in the guinea pig); general body growth ceases and the gonads become atrophic; in lactating animals, milk secretion stops. It would seem that the anterior pituitary ceases production of growth and gonadotropic hormones and prolactin in favour of increased elaboration of thyrotropic and adrenotropic principles, which may be regarded as more urgently needed in such emergencies.

If the treatment be continued with relatively small doses of the drug or relatively slight injuries, the animals will build up such resistance that in the later part of the second stage the appearance and function of their organs returns practically to normal; but with further continued treatment, after a period of one to three months (depending on the severity of the damaging agent), the animals lose their resistance and succumb with symptoms similar to those seen in the first stage, this phase of exhaustion being regarded as the third stage of the syndrome.

We consider the first stage to be the expression of a general alarm of the organism when suddenly confronted with a critical situation, and therefore term it the 'general alarm reaction'. Since the syndrome as a whole seems to represent a generalised effort of the organism to adapt itself to new conditions, it might be termed the 'general adaptation syndrome'. It might be compared to other general defence reactions such as inflammation or the formation of immune bodies. The symptoms of the alarm reaction are very similar to those of histamine toxicosis or of surgical or anaphylactic shock; it is therefore not unlikely that an essential part in the initiation of the syndrome is the liberation of large quantities of histamine or some similar substance, which may be released from the tissues either mechanically in surgical injury, or by other means in other cases. It seems to us that more or less pronounced forms of this three-stage reaction represent the usual response of the organism to stimuli such as temperature changes, drugs, muscular exercise, etc., to which habituation or inurement can occur.

HANS SELYE.

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McGill University,
Montreal, Canada.
May 18.

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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*

HANS SELYE

*M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada)*

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*Institut de Médecine et de Chirurgie expérimentales*

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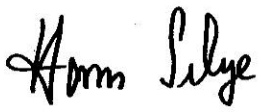

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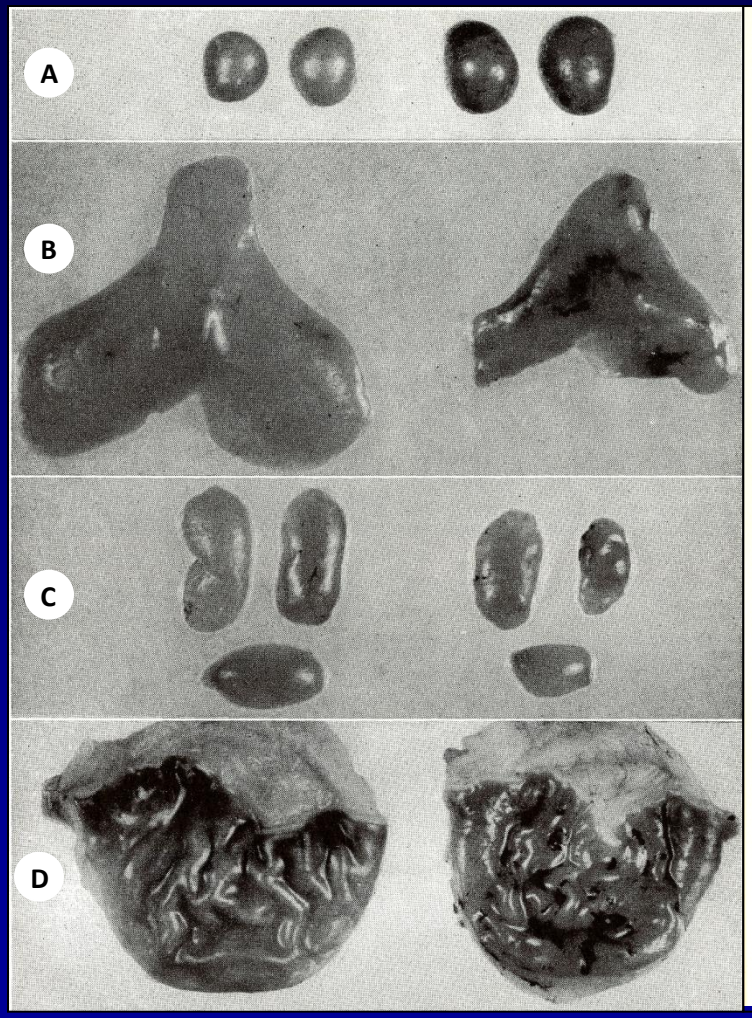
The first book of Hans Selye that contained the word "STRESS" in the title

# The typical triad of the stress reaction




*The Story*

OF THE

ADAPTATION SYNDROME

(TOLD IN THE FORM OF INFORMAL, ILLUSTRATED LECTURES)

*by*

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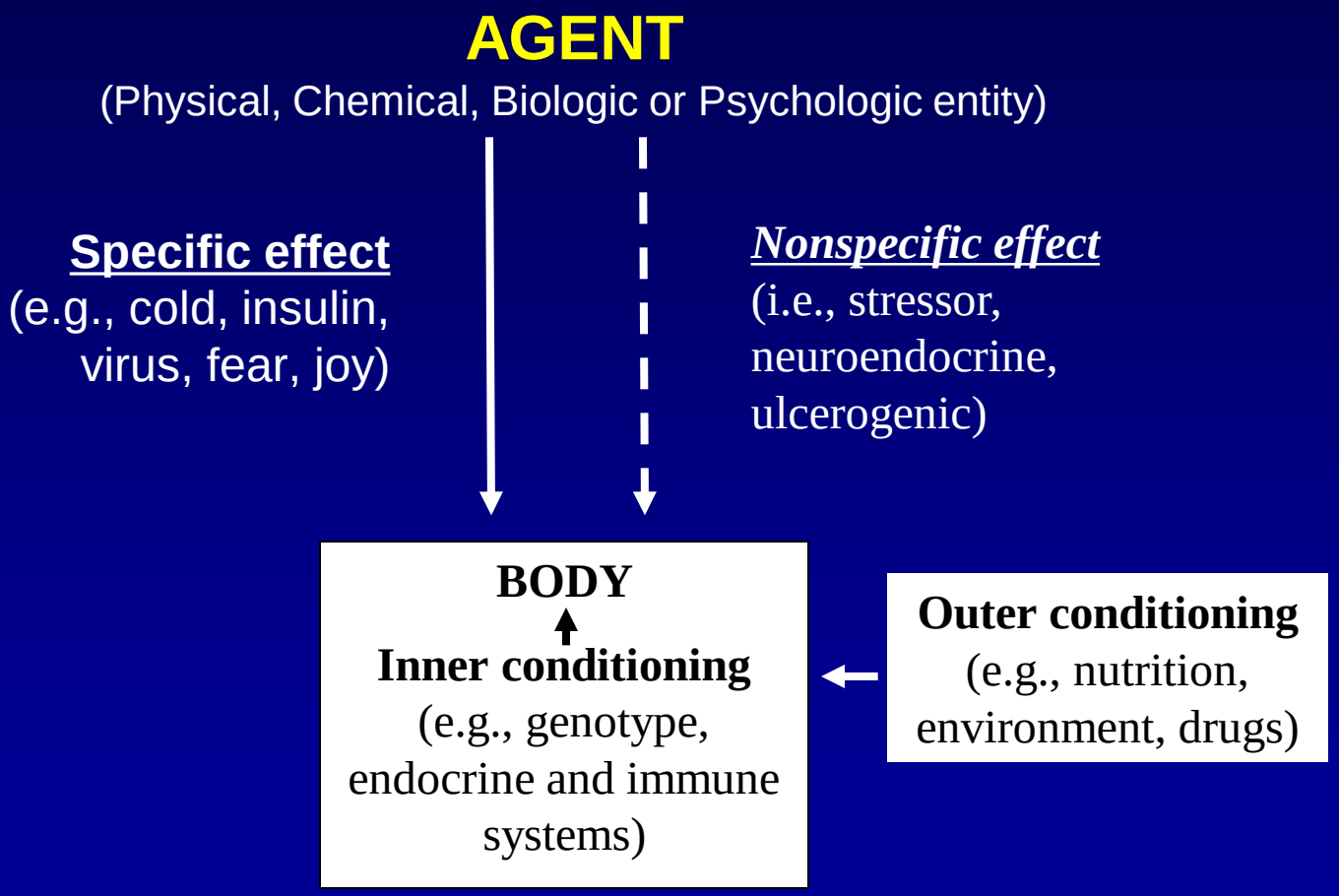
# Definitions of stress

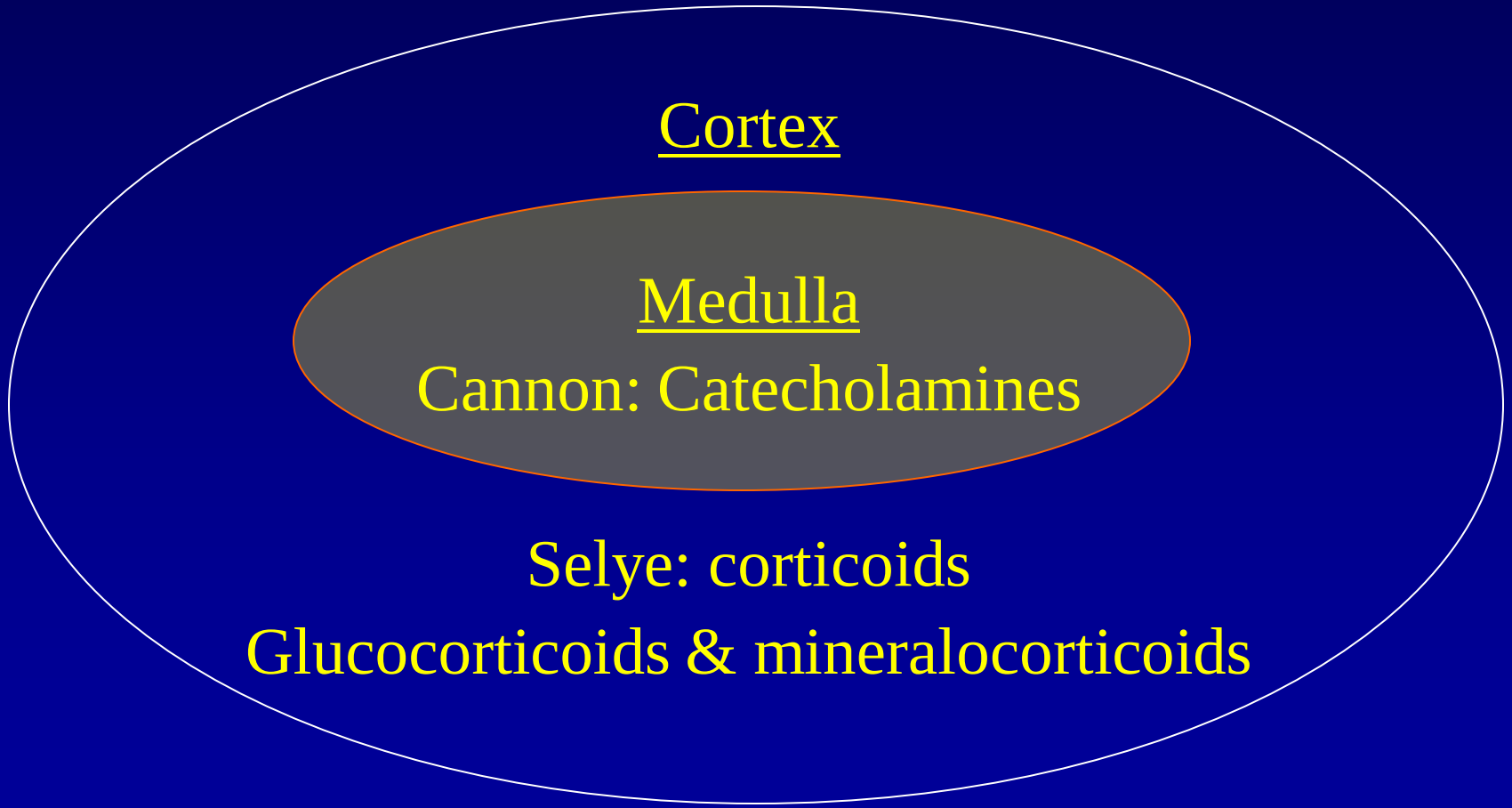
- Stress is a term in physics
- Stress vs. strain
- Early (1940s, 1950s) definition: ‘Stress is the **nonspecific** *neuroendocrine* response of the body’…
- Stress vs. stressors
- Latest (Selye, 1974): ‘Stress is **nonspecific** response of the body to any demand upon it’

# Specific and nonspecific (stressor) effects of various agents on the body




**Stressor = agent which causes stress  Stress = the phenomenon (response)**

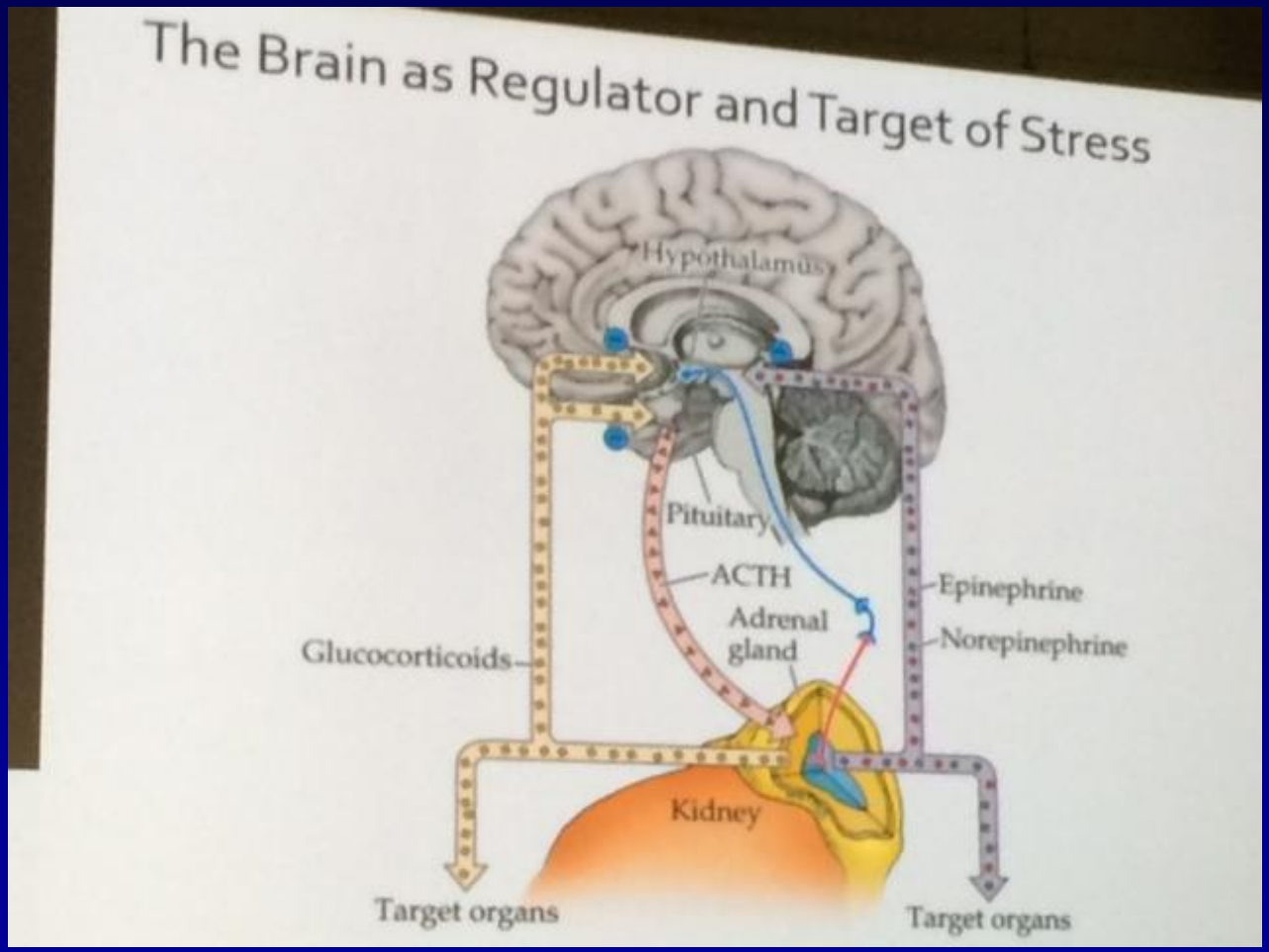
# The organ-specific contribution of Hans Selye in the development of stress concept



# The 80 years old ‘stress’ after the first article of Selye: Progress & challenges

- History
- **Progress**
  - “**Stress without Distress**” (1974)
    - **Distress** (negative, bad stress)
    - **Eustress** (positive, good stress)
- Challenges

# Dr. Illia Karatsoreos (*Indiana Univ., USA*) at the WCP 2014



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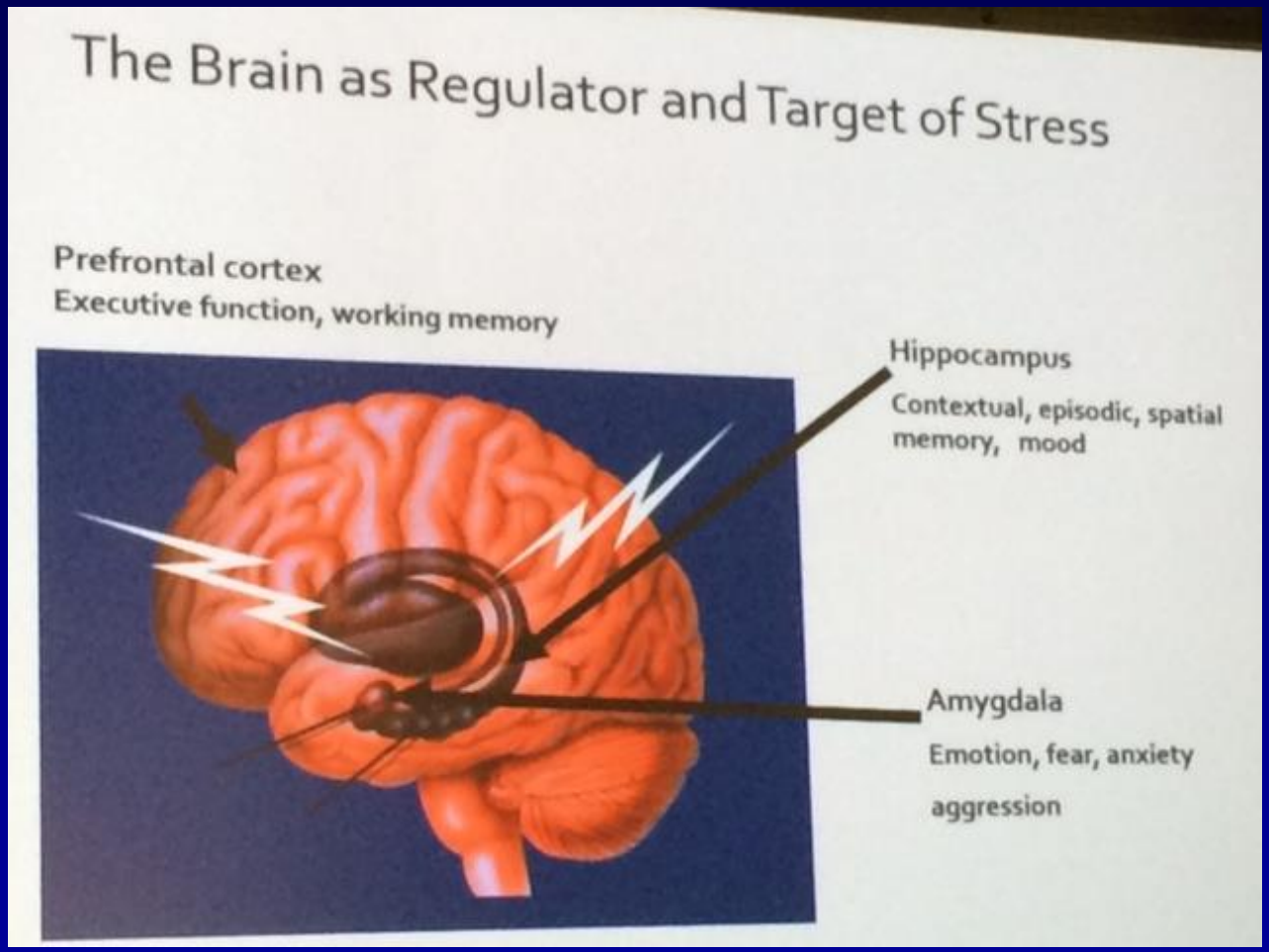
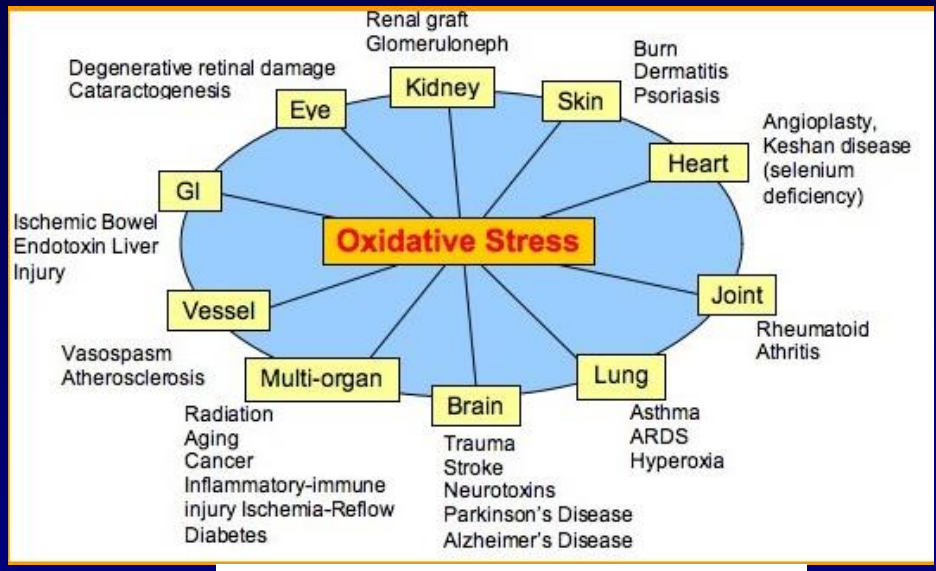
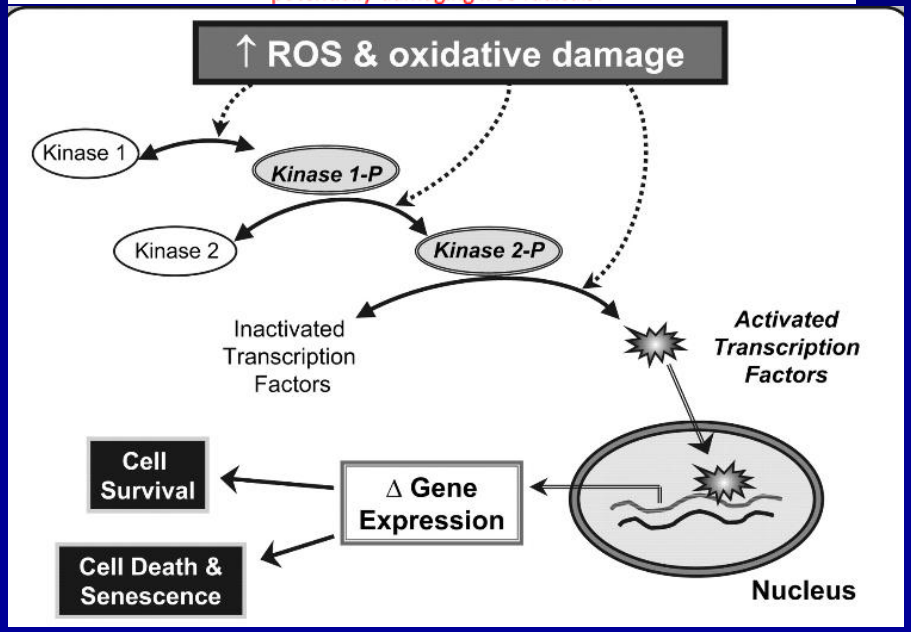
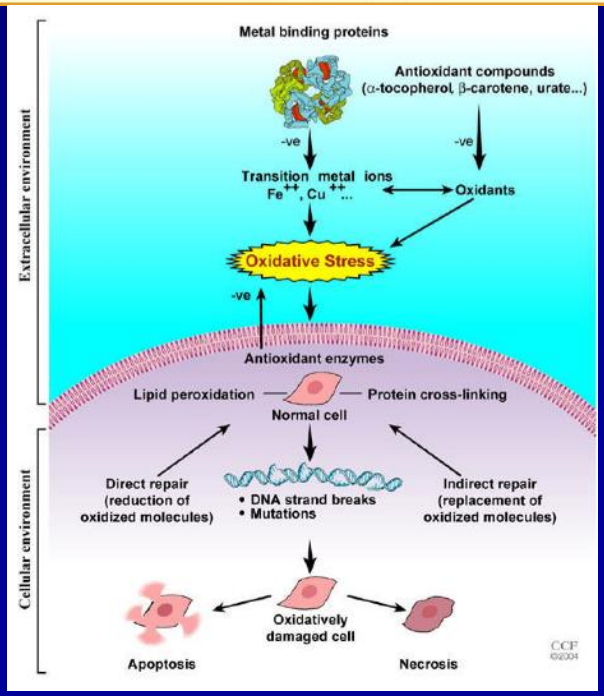


# Stress at cellular & intracellular level

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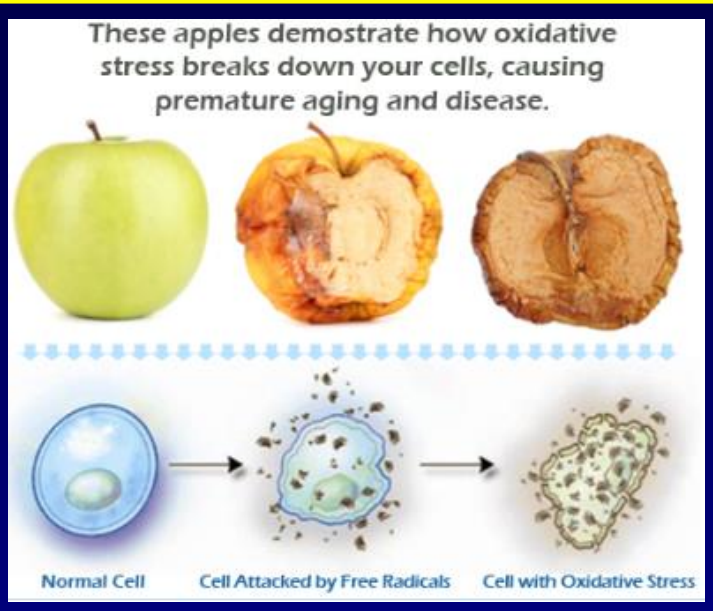


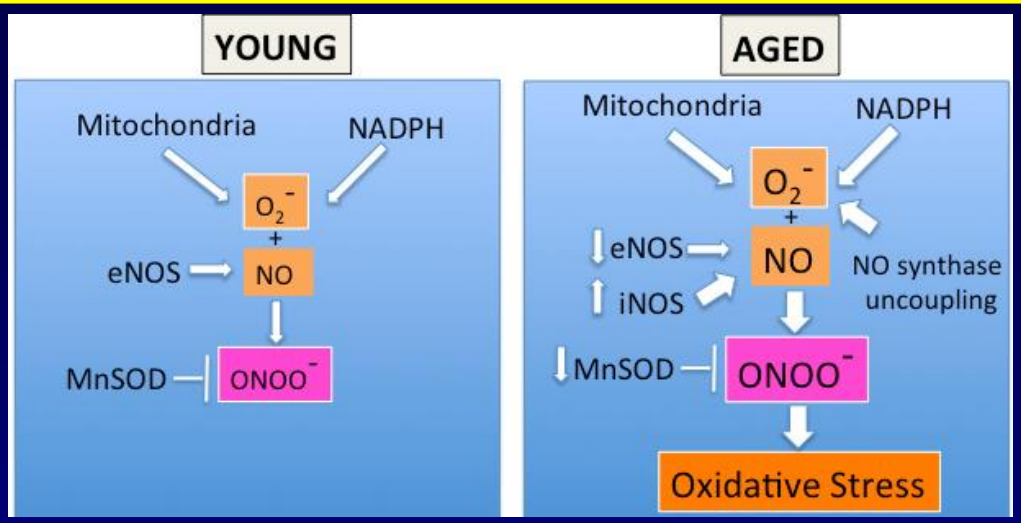


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## Metabolism: Light on leptin link to lipolysis

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Affiliations | Corresponding authors

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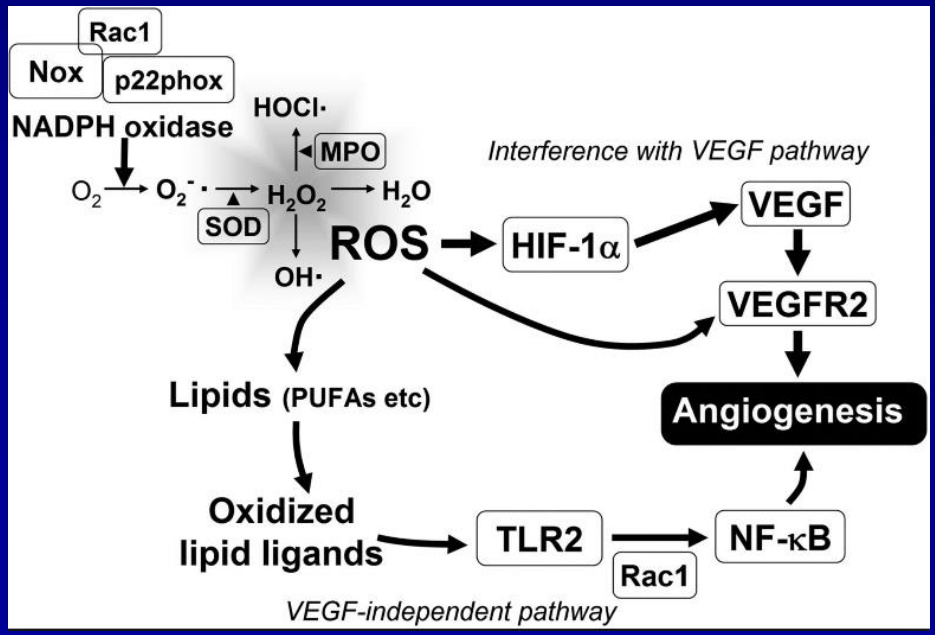

# Stress at cellular & intracellular level

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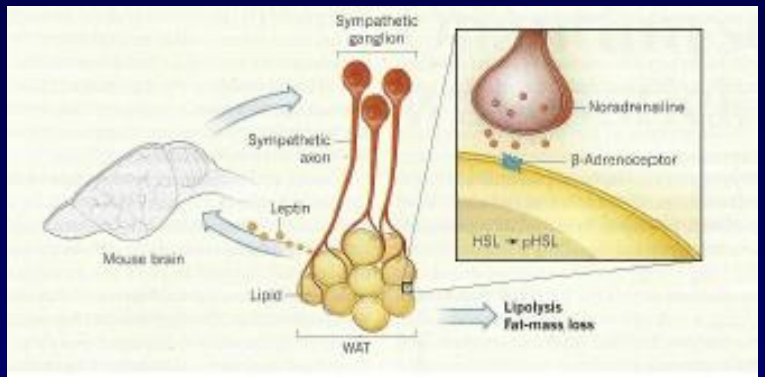


**Figure 1 | Sympathetic to fat loss.** The hormone leptin is secreted from fat tissue called white adipose tissue (WAT) in response to lipid storage. Zeng *et al.*[1] report that, in mice, leptin acts in the brain, triggering signals that activate ganglionic neurons of the sympathetic nervous system whose projections (called axons) wrap around fat cells. The neurons release the neurotransmitter molecule noradrenaline, which signals to β-adrenoceptor proteins on the fat cells. This promotes phosphorylation (p) of the enzyme hormone-sensitive lipase (HSL), triggering lipolysis (lipid breakdown) and so fat loss.

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doi:10.1038/nature12968

## Stimulus-triggered fate conversion of somatic cells into pluripotency

Haruko Obokata[1,2,3], Teruhiko Wakayama[3†], Yoshiki Sasai[4], Koji Kojima[1], Martin P. Vacanti[1,5], Hitoshi Niwa[6], Masayuki Yamato[7] & Charles A. Vacanti[1]

Here we report a unique cellular reprogramming phenomenon, called stimulus-triggered acquisition of pluripotency (STAP), which requires neither nuclear transfer nor the introduction of transcription factors. In STAP, strong external stimuli such as a transient low-pH stressor reprogrammed mammalian somatic cells, resulting in the generation of pluripotent cells. Through real-time imaging of STAP cells derived from purified lymphocytes, as well as gene rearrangement analysis, we found that committed somatic cells give rise to STAP cells by reprogramming rather than selection. STAP cells showed a substantial decrease in DNA methylation in the regulatory regions of pluripotency marker genes. Blastocyst injection showed that STAP cells efficiently contribute to chimaeric embryos and to offspring via germline transmission. We also demonstrate the derivation of robustly expandable pluripotent cell lines from STAP cells. Thus, our findings indicate that epigenetic fate determination of mammalian cells can be markedly converted in a context-dependent manner by strong environmental cues.

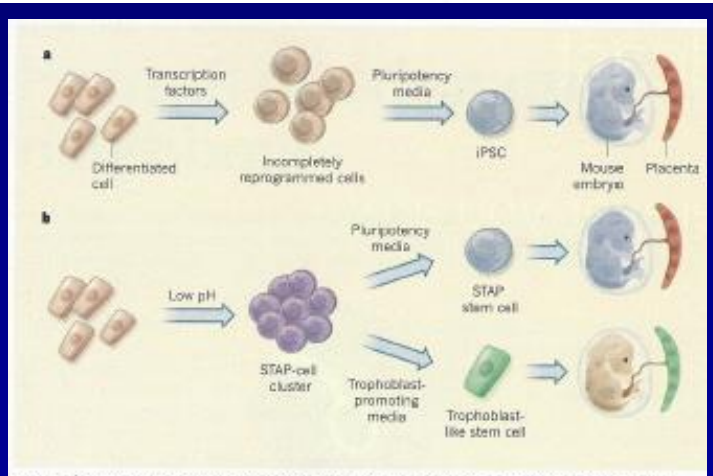



**Figure 1 | Alternative methods for dedifferentiating specialized cells.** **a**, Differentiated cells are typically reprogrammed to an embryonic-like (pluripotent) state using transcription factors and a cell-culture medium that promotes pluripotency[3]. This creates induced pluripotent stem cells (iPSCs), which can self-renew and contribute to all the cell types in a developing embryo, but not the placenta. iPSC generation occurs through a proliferative intermediate stage. **b**, Obokata and colleagues report[1,2] that dedifferentiation can also be achieved by short-term exposure of differentiated cells to a solution of low pH, a process they call stimulus-triggered acquisition of pluripotency (STAP). STAP cells do not proliferate, but subsequent treatment with pluripotency-promoting media produces STAP stem cells, which have the same properties as iPSCs. When cultured in a medium that promotes the growth of trophoblast stem cells (a placenta-generating cell type), STAP cells acquire trophoblast-like characteristics. Unlike iPSCs, the cells can contribute to the placenta.

# The 80 years old 'stress' after the first article of Selye: Progress & challenges

- History
- Progress
- **Challenges**
  - Over-use & unnecessary use of stress…
  - Do we still need to imply neuroendocrine elements?
  - What are the molecular mediators of distress vs. eustress in the brain?
  - Should we fight "oxidative" & "metabolic stress"?
  - Prevent distress or transform it into eustress!

# Stress: YES & NO

- **YES:** Response examined after at least 2-3 stressors, e.g., physical, chemical, psychologic, social stressors
- The more stressors used/examined, the more likely the response is nonspecific STRESS!
- **NO**: Any response or manifestation specific to the agent examined, e.g., shivering in cold, sweating in heat, physiologic response to a hormone (e.g., to insulin), depression over job loss…
- Any manifestation, effect that was examined/studied ONLY after a single agent (e.g., 'ether stress', 'insulin stress')

# Summary 1: The "triad of stress"

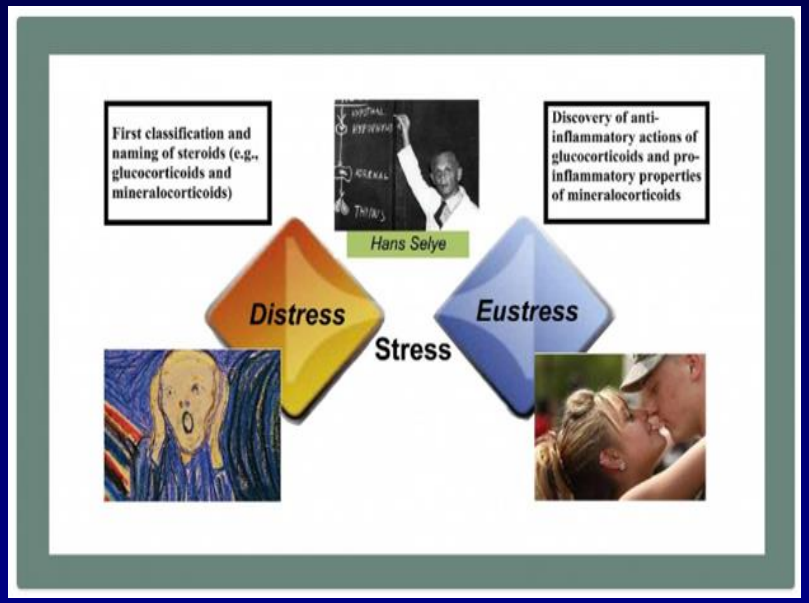
## *Selye* – Comprehensive pathogenesis

- Described the biologic stress syndrome.
- Mechanistically connected it to ACTH & steroids (i.e., glucocorticoids).
- The "triad of stress":
  - Adrenal hyperemia & hypertrophy
  - Gastroduodenal ulcers (hemorrhagic erosions)
  - Thymolymphatic atrophy

# Summary 2: Distress vs. eustress…

- Distress is usually perceived as "negative"
  - But distress may , under special modulating & conditioning factors, also stimulate creativity…
  - Examples from arts & sciences…
- Eustress might be short lasting or biphasic
  - Goal to create a lifestyle whish contains more eustress than distress…
  - Selye: "Stress is the salt of life"…


# Greetings from UCI!

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