How do you respond when you have to take an examination when you know you are unprepared? How do you respond when somebody treats you badly? How do you respond when you have to perform in public, as when giving a speech, playing a solo in band, or taking the last shot in a basketball game when your team is two points behind? You feel STRESSED, right? You know how upset you feel. But do you know what is happening in your body? … and brain?

Stress can be caused by emotional distress, physical challenges like toxins, trauma or infections, or a variety of diseases. Whatever the cause, many effects on the body are about the same. Namely, during stress a part of the nervous system, the sympathetic nervous system, becomes hyperactive. That can be a good thing, because it makes you more alert and your body is mobilized for action. The pioneer in this research was W. B. Cannon, who originated the concept of homeostasis. We have a short biography of Cannon on the PEER web site.

As shown in the diagram below, stressful conditions release two main hormones. One of the hormones is adrenalin, released from n the central zone of the adrenal gland. Adrenalin stimulates the heart, raises blood pressure and heart rate. It also stimulates the brain, promotes alertness, and improves memory.

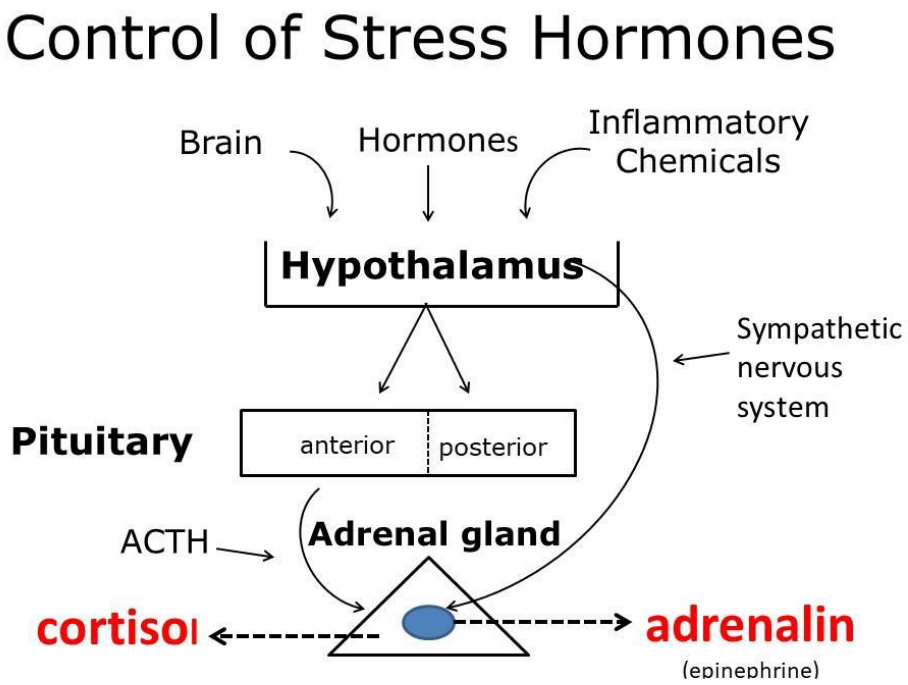
The other hormone is cortisol, released from ells in the outer part of the adrenal gland. Cortisol helps the body respond to physical damage in several ways:

- **Increases blood glucose and the supply of energy to cells,**
- **Reduces inflammation,**
- **Mobilizes white blood cells to combat infection,**
- **Stimulates the brain and promoting memory formation.**

However, the benefits disappear when the stimuli that cause adrenalin and cortisol release continue for long periods. Continual stress may lead to high blood pressure and may lead to anxiety or depression. Excessive skin problems may appear, such as acne, hives, rashes, and itching. Chronic stress may also lead to diabetes because cortisol elevates blood sugar levels. Skin becomes easily bruised, and bruises and cuts do not heal easily. Infections are harder to combat. Continual exposure to cortisol interferes with learning and memory because it causes brain damage by shrinking synaptic connections.

The synthetic versions of cortisol, known as hydrocortisone or other chemical analogs, are used medically, but only for short periods. High doses and long-term exposure to cortisol is toxic.

Here, we will meet the pioneer in stress research, Hans Selye.



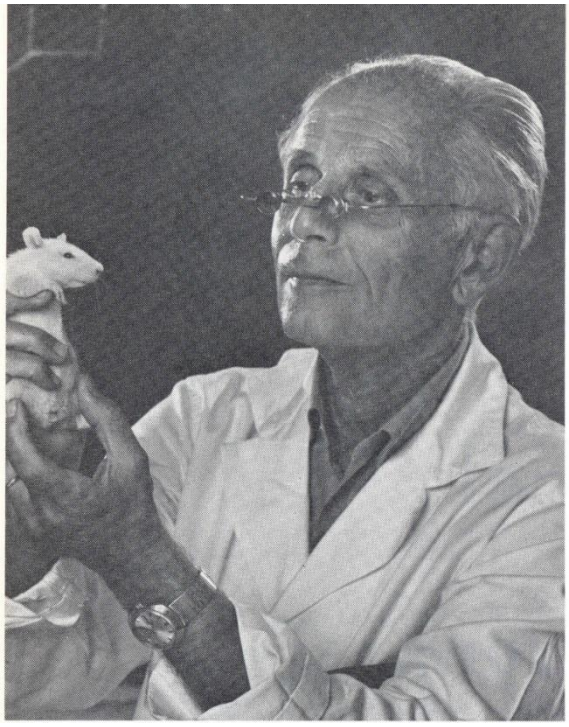


Figure 1. Selye and friend. (From *Discovery Processes in Modern Biology*).

Hans Selye

1907-1982

Are you stressed? Most everybody is at one time or another. Stress is imposed on you, perhaps by school, parents, peers, and the general demands of life. Stress makes us upset, anxious, mad, sad, and is generally unwelcome. Stress often makes us sick. Here, we will meet the pioneer in stress research, Hans Selye. His discoveries showed us what stress does to our bodies. As a result, we can learn how to deal with stress and keep it from making us mad and sad.

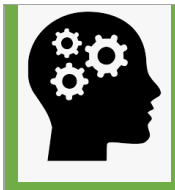
Dr. Selye was born in 1907 in Vienna Austria. Dr. Selye's family admired real excellence, and accomplishment, while they disdained mediocrity

and quitters. The family was at one time very rich, but they lost it all after his childhood in the collapse of the Austro-Hungarian Empire.

As a youngster, money was never in short supply, and he more or less took it for granted. What became important to him was learning and achievement. He said his father, who had lost his high military surgeon rank and personal fortune, told him that the one safe investment was in himself. “The only thing that is really yours, his dad said, “is what you can learn. Nobody can take that away from you without taking your life.”

As for education, it was more or less assumed that Hans would become a physician, just as his father, grandfather, and great-grandfather had. His dad owned a prosperous surgical clinic, and, being the only son, Hans was expected to take over the clinic in due course. Hans had other ideas.

He performed poorly in his high-school experience, because the curriculum was “so bookish.” He hated biology the most, because there was little lab work, and the focus was on memorizing what he considered to be boring information. Later, in college when he became exposed to exploring ideas, his attitude changed drastically. He realized the value of memorization if one used the information to explore, discover, and learn new things. From his first year in college until he graduated from medical school, he led his class in grades.



Think About It!

In your notebook, state:

- **Summarize the two stress hormones and how they are controlled**
- **List main causes of stress.**
- **What were his parents’ attitudes about how to be successful?**

Dr. Selye spent the bulk of his career at the University of Montreal in Canada. The author of this biosketch visited his lab and described it this way:

It was a crisp Canadian, October morning at the University of Montreal, and I was visiting the lab of Dr. Hans Selye to talk him into writing a chapter for my book, “Discovery Processes in Modern Biology.”

I doubt if any scientist has a lab quite like that of Dr. Selye. His lab occupied the entire 7th and top floor of the building. Along each of the four outside walls of the building were offices

for students and post-docs. In the center of the floor were labs and a huge personal library staffed by several full-time librarians. His library contained over a half million reprints of publications by other scientists. One whole room is *occupied totally by card catalogues.*

Upon arriving, I was greeted by a receptionist and a few secretaries, and then led to a huge guest book. A significant number of the several hundred scientists and famous public figures who have visited Hans Selye have autographed pictures lining both sides of most of the halls in this large complex. One of those pictures was that of Roger Guillemin, one of Selye's graduate students who won the Nobel prize for discovering hormones released by nerve cells that control the secretion of the pituitary gland. Also lining the halls are displays that summarize some of the past research accomplishments of Dr. Selye and his colleagues. One wall has a 10-foot wide world map, with red pins and string pointing all over the world, showing countries of origin of the many scientists who have actually worked in Selye's lab.

I saw Selye's conference room, carpeted and draped, and what appeared to be a 30-foot conference table. The "tour guide," a graduate student, showed me Selye's medal cabinet, a display mounted on red velvet background of his more than 70 medals (one denoting him as Honorary Citizen of my state, Texas).

I saw Selye's famous post mortem room, where he personally critiqued every necropsy of experimental animals, at least up until about the last year. Selye's very special talent was seeing things in animals, alive or dead, that others did not see.

And then I met Selye in his office. What does one say to a legend? This quiet, gentle, and aging man seemed to sense my embarrassment, and quickly engaged me in conversation about my own work. We talked about biological research and discovery processes. He showed me his office, one wall of which was lined with books-all written by him! He showed me draft manuscripts of his latest project, about a 10-volumes on hormones. Here he was near the end of his incredibly productive career, beginning a project of such mammoth scope that no one man had attempted such a thing before.

Selye began his higher education at the German University of Prague. This was followed by enrollment at the University of Paris, University of Rome, and back again to his first university. There he earned the M.D. degree, a Ph.D. in Chemistry, and a Doctor of Science degree.

It was in medical school that Hans realized his interest in research. The professors he sought out were the ones who were engaged in research. What he really wanted to know was what "made these professors tick." What was the nature of their successes? How did they deal with frustrations and failures? What kinds of attitudes and talents does one need to pursue a life of research? I was also interested in such questions, which was one of the reasons I wanted to visit with Selye.

While a medical student, Selye was struck by noticing that many sick people had similar symptoms, even though they had different diseases. It seemed, as he put it, that the symptoms were symptoms of "just being sick." He wondered, "Is being sick a sickness of its own?" Haunted by this question, he spent his life discovering that multiple diseases do create a common

disease, a disease of being chronically stressed. This chronic response is a stress disease that can be superimposed on whatever abnormal situation caused the original disease. The symptoms are "nonspecific" (not characteristic of any one disease). Patients with chronic disease, of whatever cause, “looked sick” to him: they typically had a coated tongue, complained of diffuse aches and pains in the joints and intestinal disturbances with loss of appetite. Many had fever, sometimes with mental confusion, an enlarged spleen or liver, inflamed tonsils, and other signs.

Later, when he was working in the Biochemistry Department at McGill University, Selye discovered the clues to the "stress disease." He was trying to isolate a new ovarian hormone in extracts of cattle ovaries. All the extracts, when injected into lab mice or rats caused a similar response: enlargement of the adrenal cortex (the outer part of the gland), ulcers in the digestive tract, and shrinkage of the thymus and lymph nodes. His first thought was that the syndrome was due to a new hormone he had discovered. But then he learned that other kinds of extracts, such as from the pancreas, caused a similar syndrome when injected into lab animals. “What is going on here?” he asked himself. Obviously, this was some kind of nonspecific response. But to what? An answer occurred to him. Maybe the cause was tissue damage. He tested the idea of tissue

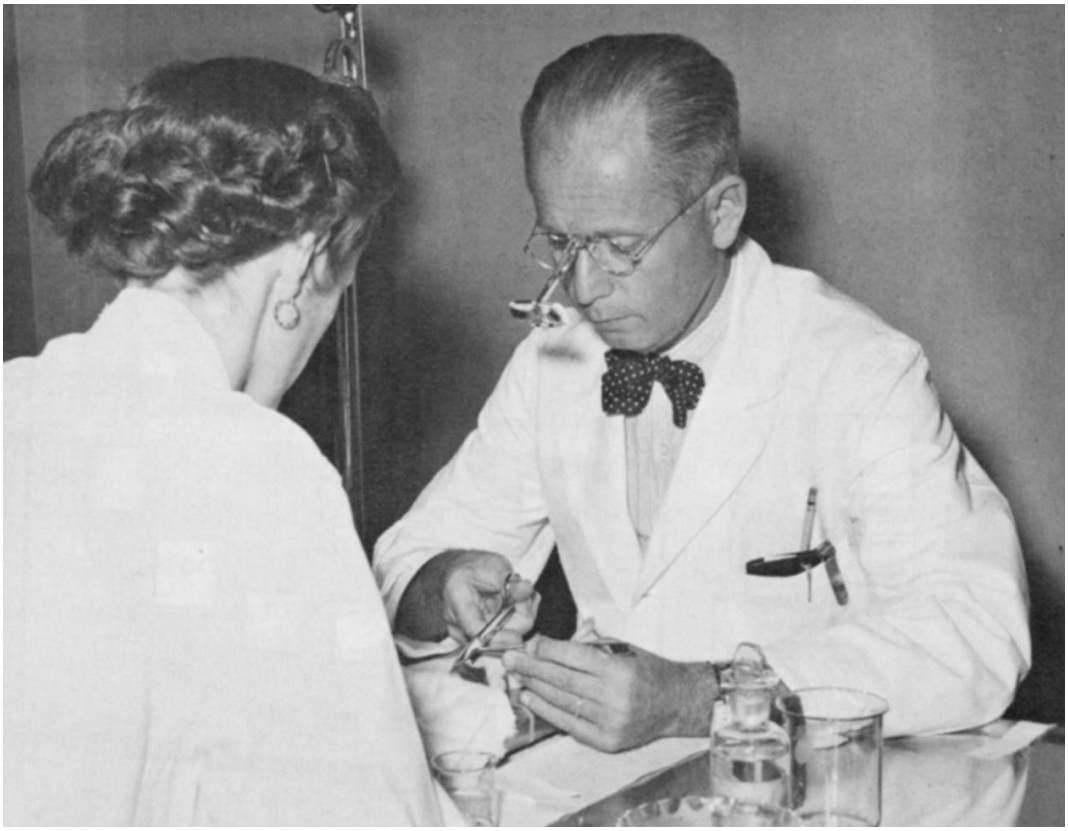


Figure 2. Dr. Selye and assistant performing an autopsy on a lab rat to observe stress-induced changes. (From *Discovery Processes in Biology*).

damage by injecting other lab animals with low doses of formalin, a chemical known to irritate all kinds of tissue. The same nonspecific symptoms occurred. Eureka! However, he did not see this as any great discovery. He saw it as failure to discover a new hormone. What he eventually came to realize was that he had discovered the body's main non-specific response to tissue damage.

Dr. Selye thought he had failed, but he knew failure was a waste if he didn't learn from it. So, when he thought more about his observation, he realized he was looking at the results in the wrong way.

One of the first things Dr. Selye did was to test a variety of substances that cause tissue damage, such as excess cold or heat, X rays, mechanical trauma, pain … anything that was noxious. They all caused the similar stress responses. His first research report, in 1936, was titled, "A Syndrome Produced by Diverse Nocuous Agents." He called this an "alarm" reaction to acute tissue damage. He later discovered that this "alarm" reaction was the first stage of a General Adaptation Syndrome (G.A.S.). The syndrome is a set of physiological responses to stress that follows the sequence of alarm, adaptation, and exhaustion.

Selye suffered his own stress from the criticisms of many of his colleagues who told him he was wasting his time studying stress responses. They were too nonspecific. This was not an accepted topic in hormone research, which is what Selye was expected to be doing. A prominent critic was Walter Cannon, who at the time did not think the adrenal cortex and pituitary were important in stress responses. Cannon, of course, emphasized the role of the sympathetic nervous system, because that was what he had shown was involved in the reaction to stress.

Selye took heart however in the realization that his research was important enough to be dignified by critics who argued against it. Sometimes it is better to be criticized than ignored. The criticism spurred him on to prove them wrong. Selye was shaken from his dismay and failure by a famous Canadian scientist, Sir Frederick Banting, who visited labs all around Canada. When he visited Selye's lab and learned of his findings and ideas, Banting was impressed and encouraged Selye to continue. Banting even arranged funding for Selye to continue his research.

Selye went on to do experiments where noxious agents were given repeatedly. He realized that if tissue damage is sustained, the alarm reaction cannot continue. The adrenal gland, for example, now shrinks out of exhaustion. It can no longer make its cortisol. Others had shown that the secretion of cortisol was stimulated by a peptide hormone released from the anterior pituitary, adrenal cortical stimulating hormone (ACTH).

So now, Selye realized that ACTH must be part of the G.A.S. Moreover, since the pituitary gland is regulated by neurons in the hypothalamus part of the brain, they also be involved in G.A.S. In fact, it is this brain connection that explains why negative emotions cause the stress signs of the G.A.S. One of Selye's PhD students, Roger Guillemin, won the Nobel

Prize in 1977 for discovering hypothalamic peptides that acted like hormones by acting on the anterior pituitary gland. Guillemin worked out the structures of thyroid hormone releasing factor and luteinizing hormone releasing factor. He did many studies on the ACTH releasing factor, but his competitor Victor Schally was the one who isolated and purified it.

Looking back on his career, Selye told me what he learned about the scientific process. On numerous occasions he rejected grant support from drug companies who wanted him to do routine tests of their products in development. Somebody has to do that, but Selye always worried that it would distract him from his drive to discover. Most important, as he put it, was, "To give meaning and direction to life, we must have some long-range aim, something in the distance that we can work for."

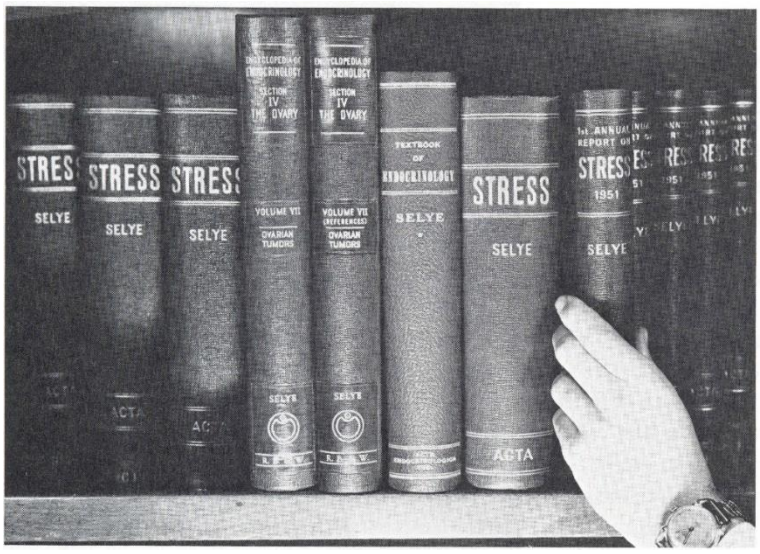


Figure 3. Some of the 33 books and 1,600 research reports that Hans Selye published. (From Discovery Processes in Biology).

He has also commented on the need to deal effectively with criticism. The people that criticized him, like Cannon, suffered criticism of their own work. Selye learned that he had to take the bad with the good, that in science criticism is part of the game, a necessary factor in identifying ideas that are false in order to establish what is true. Failure and criticism should not be taken too personally.

Finally, he reflected on what it takes to increase the likelihood of discovery. He explained that sometimes raw intelligence gets in the way. The first requirement is a great capacity to dream; the second is persistence—a faith in the dream. Faith is important in science. It spurs one on to discover.

Sources:

Klemm, W. R. (1976) Personal interview and visit to Dr. Selye's laboratory

Klemm, W. R. (1977) *Discovery Processes in Modern Biology*. Huntington, N.Y.: Krieger