

HEALTH AND STRESS

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REMEMBERING HANS SELYE AND THE BIRTH OF "STRESS"

KEYWORDS: "They all just looked sick", Johns Hopkins "sardine period", "A Syndrome Produced By Diverse Nocuous Agents", *Encyclopedia of Endocrinology*, Nobel Prize for cortisone, the "O.K. rule" for intercourse, *The New Yorker Magazine*, "The Renaissance in Endocrinology", *AMA Glandular Physiology And Therapy* textbook

My choice for "The Most Unforgettable Character I Ever Met" feature that regularly appeared in the *Reader's Digest* would have to be Hans Selye. However, he might not be high on many other lists because of his seemingly aloof attitude. His father was a surgeon in the Imperial Austro-Hungarian Army, and his early upbringing may have resulted in an authoritarian, Prussian demeanor that was often interpreted as an air of arrogance. Hans was born in 1907 in Komarõm, a small town in the Hungarian part of the Empire, midway between Vienna and Budapest. He attended school at a Benedictine monastery, and since his family had produced 4 generations of physicians, entered the German Medical School in Prague at the age of 17.

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**Life At Selye's Institute Of Experimental
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While in medical school, Selye noted that patients suffering from very different diseases often exhibited the same signs and symptoms in the first days of their illness. They all had low-grade fevers, feelings of malaise, fatigue, generalized aching, and "they just looked sick". He was excited about the possibility of studying the biochemical changes and mechanisms that were responsible for these common findings, since he thought this might possibly lead to some form of treatment or relief.

He made an appointment to speak to the Chairman of the Department of Physiology to ask if he could study this in his laboratory on weekends or free time after school. The Chairman's full name, including titles, was Hofrat

Professor Doktor Armin Tschermak Edler (Nobleman) von Sysenegg. Since that was quite a mouthful, it was concluded that at least his highest title should be used, and he expected to be addressed as "Herr Hofrat" (Counsel to the Imperial Court.) Selye, who was then 19 and unaware of this, innocently called him "Herr Professor". Apparently, that was the only part of his enthusiastic presentation that made an impression, since after he had finished, the response was "Well, if you are that chummy, why don't you just call me by my first name, Armin." Even after profuse apologies, his request was rejected as being so juvenile that it was not even worth discussing. He was told that obviously, if a person is sick, he looks sick, just as if he is fat, he looks fat. He was warned not to bring the subject up again and to concentrate on studying for his exams. Selye obeyed this edict, graduated first in his class, and two years later, received a doctorate in chemistry.

Because of his obvious talents, Selye was awarded a Rockefeller scholarship to study at Johns Hopkins. He arrived in Baltimore in 1931, rented a cheap room with a kitchenette near the University, and learned how to cook for himself so that he could save some money from his \$150 monthly stipend. He subsisted mostly on canned foods, and often referred to this as his "sardine period", since a large tin was a bargain at 10 cents, and he ate them daily for months. The other postdoctoral students warmly accepted him, and sympathetic faculty wives, who felt sorry for "the poor lonely foreign students", constantly arranged parties and social events so that they could meet people. Although Selye spoke English fairly well, he quickly realized that Americans had their own lingo. On one occasion, when he met the very attractive daughter of a prominent professor at a party, he asked if they could meet again to go to a movie or dinner, and offered to walk her home. Her response was "Yes, but would you give me a ring first?" Selye was petrified, since he thought she meant an engagement ring, and had heard many stories of the strict enforcement of "breach of promise" laws in the U.S. He congratulated another girl on her beautiful complexion by saying that her "hide" was of the finest quality, which she did not take as a compliment. Unfortunately, there was no distinction between hide and skin in any of the many languages Selye spoke.

He also had difficulties adapting to faculty life at Hopkins, having been reared in a formal academic European environment where there were rigid class distinctions, much like the military. Full professors were respected and obeyed as if they were Generals in the Army, and Department Heads were demigods. Selye was appalled at the sight of such distinguished middle-aged and older individuals playing charades and acting in an undignified fashion at faculty parties, to which house staff and even medical students were invited. Jackets and ties were discarded, and everyone often seemed to be on a first name basis. He could never conceive of Professor Hofrat or his other teachers acting in such a degrading way, and suffered a severe case of culture shock and confusion. He considered returning home, but was

told by friends that Canada was more European, traditional and sedate. After making a few inquiries, he found that he could transfer the second half of his fellowship to McGill University in Montreal to work under the renowned biochemist J. B. Collip. Although fluent in Parisian French, he also found out that Québécois, a patois version spoken in Montreal could be quite different, but quickly adapted. He ultimately joined the McGill Faculty, became a Canadian citizen, and in 1945, moved to his own Institute of Experimental Medicine and Surgery at the University of Montreal.

Selye once told me that he never felt he really had any personal nationality. He spoke fluent German, Hungarian, Czech, Slovak, French, and English, since each had been his national language at one time or another. Based on personal experience, I can confirm that he was also comfortably conversant in Russian, Spanish, Greek, Italian and Portuguese, and could understand Swedish and a few other languages if they were spoken slowly. While his first name was Austrian, his surname was Hungarian. He was looked down upon as an Austrian when he was in Hungary, and vice versa. When the Empire collapsed in 1918, he became Czechoslovakian without ever moving out of his house. The Czechs and the Slovaks had numerous disagreements with each other, but they unanimously detested both the Austrians and Hungarians. After he became an international celebrity, Czechoslovakia, Austria, Hungary and Canada, all sought to claim him as their own. He readily accepted these accolades, but confided in me that he was most proud of his Magyar Hungarian heritage. He was particularly fond of Hungarian "Bull's Blood", and on several occasions when I visited at his home, we consumed liberal amounts of this rich red wine, along with the superb Hungarian goulash he loved to make.

As instructed, Selye had not thought any more about the syndrome of "just being sick" that intrigued him in Medical School, but by a strange twist of fate, it resurfaced a decade later when he transferred his Fellowship to McGill. At the time, only two types of female hormones had been identified, but Professor Collip thought there was a third, and assigned Selye to this quest. He was sent to the slaughterhouses with a large bucket and told to retrieve as many cow ovaries as possible, which Collip then reduced to various extracts for Selye to inject into female rats for several days or weeks. The animals would later be autopsied to look for any changes in their sex organs or other tissues that could be attributed to this presumed "new" ovarian hormone. However, no such effects could be demonstrated and what was more disheartening, many of the rats became severely ill, and some died. Selye was also a superb and meticulous pathologist, and although there were no changes in the ovaries or breasts, he noted that **all of these rats showed enlargement of the adrenals, shrinkage of the thymus and lymphoid tissues, and ulcerations in the stomach**. This made no sense, and he searched for some explanation. One possibility was that these changes might be due to some chemical contaminant in Collip's concoction.

Right in front of him was a bottle of formaldehyde, a toxic substance used to fix tissues for microscopic study. On a hunch, he injected liberal amounts of formaldehyde into several rats, and was amazed to find that it resulted in the identical pathological changes in these specific tissues and organs.

He began to wonder if other noxious substances or stimuli might also produce these same three findings, and what ensued is now history. He exposed rats not only to powerful chemicals, but also the frigid Canadian cold winter, by leaving them exposed on the wind swept roof of the McGill medical building. Others were put in a revolving barrel-like treadmill contraption driven by an electric motor, so that they had to constantly run to stay upright. Sure enough, all developed the same pathologic picture in the adrenals, lymphoid tissues, and stomach. Selye viewed this syndrome as a nonspecific response to what he referred to as "biologic stress". He published these findings in the form of a 74-line letter to the editor of the British journal *Nature* in 1936 entitled "A Syndrome Produced by Diverse Nocuous Agents". But the **word "stress" had to be deleted since it was commonly used to mean nervous strain, especially in women. The editor thought this could create confusion, so Selye substituted "Alarm Reaction"** to describe this response, which he viewed as a coordinated mobilization of the body's defensive mechanisms.

The General Adaptation Syndrome And The "Diseases Of Adaptation"

In subsequent studies, he found that the same changes could be produced by other noxious challenges and stimuli. Animal activists were less vocal at the time, and many of these experiments could never be performed today, including exposing rats to brilliant lights after their eyelids had been sewn back, constant deafening noise, making them continuously swim to the point of exhaustion to avoid drowning, and intense psychological frustration that bordered on torture. He also showed that the characteristic pathologic **"Alarm Reaction"** changes occurred not only in rats, but mice, rabbits, dogs, cats, and other animals subjected to such acute insults. Selye then studied the effects of longer exposure to noxious but nonlethal stimuli, noting that this resulted in a **"Stage of Resistance"**, during which the body's defense mechanisms were maximized to adapt to these threatening challenges. However, if they persisted, a final **"Stage of Exhaustion"** ensued, with deterioration and death. He termed this three-stage response, **"The General Adaptation Syndrome"**.

Detailed autopsies performed during the various stages of this syndrome revealed gross and microscopic changes identical to those seen in patients with arthritis, kidney disease, hypertension, coronary heart disease, and gastrointestinal ulcers. Selye suspected that perhaps "stress" might also cause these disorders in humans as well, and therefore considered them to be **"Diseases of Adaptation"**. ("Diseases of Maladaptation" would have actually been more appropriate.) After thousands of additional experiments,

he found that he could replicate many of these disorders selectively by sensitizing or conditioning the animals through certain dietary or hormonal manipulations, and/or subjecting them to different stressors.

He subsequently traced the pathways and mechanisms that were responsible for the changes seen in the "Alarm Reaction", and demonstrated that they were due to increased pituitary stimulation of the adrenal cortex to produce hormones that reduced inflammation. This explained why the adrenals were enlarged. Similarly, the stomach ulcers and lymphoid tissue shrinkage were due to the increased amounts of these cortisone-like hormones. If he removed the pituitary gland, these manifestations of damage in different organs and structures did not occur. He reasoned that if he could show how such injuries were caused, then perhaps he could also find a way to prevent or treat the resultant diseases more effectively.

Selye's innovative concepts of stress and Diseases of Adaptation were quite radical. As a result of Pasteur's research and Koch's Postulates, physicians had now been taught that each disease had its own, very specific cause. Tuberculosis was caused by the tubercle bacillus, pneumonia by the pneumococcus, rabies, anthrax, and cholera by other microorganisms etc. **What Selye was proposing was actually the complete converse of this.** He had now demonstrated that **very different, and even opposite physical challenges**, such as extremes of heat and cold, as well as severe emotional threats, **could indeed produce identical pathological changes** in certain organs and structures. While each of these might also have their own specific signatures, such as a burn, or frostbite, they all caused the identical non-specific changes in the adrenal, stomach, and lymphoid tissue he had first seen following injection of the new ovarian hormone extract. Perhaps this also explained the curious, but very common, syndrome of "just being sick" he had observed as a medical student in the early stage of illness in patients who later eventually developed very different diseases.

Hooke's Law, Strain, *Le Stress*, *La Stresse*, *Pathos*, *Ponos* And Stressor

Selye selected the word "stress" to describe this phenomenon, and defined stress as "the non-specific response of the body to any demand for change". In many respects, this turned out to be a disastrous decision that haunted him the rest of his life. Stress had evolved from the Latin *strictus* (tight, narrow) and *stringere* (to draw tight). This became *strece* (narrowness, oppression) in Old French, and *stresse* (hardship, oppression) in Middle English. In vernacular speech, and in Selye's opinion, stress represented a contraction or variant of distress, which would have been appropriate. Unfortunately, he was unaware that stress had been used for centuries in physics to explain elasticity, the property of a material that allows it to resume its original size and shape after having been compressed or stretched by an external force. As expressed in Hooke's Law of 1658, the magnitude of an external force, or stress, produces a proportional amount of

deformation, or strain, in a malleable metal. The maximum amount of stress a material can tolerate before becoming permanently deformed is its elastic limit. This ratio of stress to strain is a characteristic property of each material, and is called the modulus of elasticity. Its value is high for rigid materials like steel, and much lower for flexible metals like tin. Selye often complained to me that, had his knowledge of English been more precise, he would have gone down in history as the father of the "strain" concept.

This also created considerable confusion when his research had to be translated into foreign languages. There was no suitable word or phrase that could convey what he meant, since he was really describing strain. In 1946, when he was invited to give a keynote address at the prestigious *Collège de France*, the academicians responsible for maintaining the purity of the French language struggled with this problem for several days. They eventually decided that a new word would have to be created and apparently, the male chauvinists prevailed. Thus, *le stress* was born, quickly followed by *el stress*, *il stress*, *lo stress*, *der stress* in other European languages, and similar neologisms in Russian, Japanese, Chinese and Arabic. Stress is one of the very few words you will see preserved in English in these latter languages. As usual, according to Charles Dickens and linguistic authorities, "the Greeks had a word for it". Twenty-four centuries previously, Hippocrates had written that disease was not only *pathos* (suffering), but also *ponos*, (toil), as the body fought to restore normalcy. While *ponos* might have sufficed, contemporary Greeks also settled on "stress".

Selye's concept of stress and its relationship to illness quickly spread from the research laboratory to all branches of medicine, and stress ultimately became a "buzz" word in vernacular speech. However, the term was used interchangeably to describe both physical and emotional challenges, the body's response to such stimuli, as well as any resultant pathologic changes. Thus, an unreasonable and over demanding boss might give you heartburn or stomach pain, which eventually resulted in an ulcer. For some, stress was the bad boss, while others used stress to describe either their "agita" or a bleeding peptic ulcer. Because it became clear that most people viewed stress as some unpleasant threat, he had to create a new word, "stressor", in order to distinguish between stimulus and response. Even Selye had difficulties when he tried to extrapolate his animal research to humans. In assisting him to prepare his *First Annual Report On Stress* in 1951 (See page 12), I included the comments of one critic that appeared in the *British Medical Journal*. Using verbatim citations from Selye's own writings, he complained that **"Stress, in addition to being itself, was also the cause of itself, and the result of itself."**

I first met Selye when he was completing his magnum opus, *Stress*. He was already internationally regarded as one of the world's leading authorities on endocrinology, steroid chemistry, experimental surgery and pathology. Selye did everything on a grandiose scale. He had singly

authored the first *Textbook of Endocrinology* in 1947, and the previous year had published several volumes of his proposed *Encyclopedia of Endocrinology*, covering every aspect of this subject. *Stress*, which was published in 1950, was a huge book of over 1000 pages containing more than 5000 references. However, its size paled in comparison to the 27-volume *Encyclopedia of Endocrinology*. Section IV, *The Ovary*, included Volume VII, *Tumors Of The Ovary*, actually consisted of two mammoth books. Despite their stuffy, and scholarly nature, Selye's sense of humor is evident in both, as illustrated and discussed on the last page of this Newsletter. Section I of the Encyclopedia, entitled *The Steroids*, consisted of two huge volumes containing the formulae of all steroids that had been identified by 1946, as well as the chemical and biological activities of each one, citing specific references. It was never completed, since Selye had to continually make additions as new compounds and their physiologic activities were constantly being discovered.

Kendall and Hench at The Mayo Clinic received the Nobel Prize in 1950 for their discovery of cortisone and its dramatic effect on rheumatoid arthritis. Many felt this honor should have been shared with Selye, since he had been nominated along with them for predicting the existence of such a steroid, as well as its probable formula. Although he received numerous international awards and accolades, he was always bitter about not having received the Nobel Prize, **despite having been nominated ten times**. Morris Fishbein, the powerful Editor of the *Journal of The American Medical Association* had publicly gone on record as saying he was an odds on favorite. However, as will be explained in a subsequent Newsletter, Selye's seemingly authoritarian and aloof attitude may have antagonized many of his powerful colleagues, including Walter Cannon, Dwight Ingle and George Thorn, who had other theories. This proved to somewhat awkward when one of his Fellows, Roger Guillemin, who was at the Institute in 1951, shared the 1977 Nobel Prize in Medicine for his characterization of the endorphins. However, this was not based on research done under Selye's aegis.

Selye was perceived as being so stiff and formal, that his keen wit and sense of humor were generally unappreciated, although it was readily apparent in his writings. He was frustrated by the indices of some pedantic texts, since when he looked up a reference, instead of citing the page number, he was often referred to another heading, which on occasion would suggest looking under still another topic. Consequently, in the Index of his 1947 *Textbook Of Endocrinology*, there is an entry entitled, "**Selye; see: what next?**" If you follow this instruction, you will find, "**What next; see: Selye.**" Another index entry was, "O.K." rule: 816. The discussion on page 816 referred to the fact that conception is unlikely to occur around or during the menstrual period. As Selye explained,

It is therefore customary to refer to the pre- and post menstrual days as the 'safe period,' an expression which is perhaps not entirely

beyond criticism, since **it takes for granted that intercourse is decided upon for motives other than reproduction.** This relationship between fertility and the phase of the menstrual cycle was mainly clarified by the Japanese physician Ogino, and the Austrian investigator Knaus, and hence it is sometimes designated as the Ogino-Knaus or 'O.K.' rule. **The writer disapproves of the use of an abbreviation in this instance.** (Emphasis supplied)

He was a voracious reader, consuming everything from the most technical and esoteric journals in 8 languages, to popular magazines and pulp fiction, which he did with lightning speed. He read as fast as most people could skim, and could skim a book in almost the time it took to turn the pages. However, he seemed to retain as much from skimming a page, as most of us would from reading it, because of his amazing photographic memory. He could often quote almost verbatim part of an article he had seemingly only glanced at months before. His favorite lay publications were *The New Yorker Magazine*, with its cartoons by Price and Arno, and some obscure Hungarian publication similar to *The National Enquirer*. He had a fetish about retaining copies of every article in any scientific or lay publication remotely dealing with stress, but it didn't stop there. He would write away for reprints of all the pertinent citations listed in an article, retrieve the relevant references from those articles when they were received, and then send away for these reprints. He repeated this process over and over, which resulted in a never-ending chain of reprint requests in different languages from all over the world.

Selye's Symbolic Shorthand System And Surgical Innovations

The problem was in deciding where and how to file this mountain of material. If it had to do with cold stress in hypophysectomized and adrenalectomized rats on a high sodium diet to determine the development of hypertension and/or cardiac enlargement, should he make seven copies to store separately under cold stress, hypophysectomy, adrenalectomy, combined hypophysectomy-adrenalectomy, high sodium diet, hypertension, and cardiac hypertrophy? To overcome this problem, he devised his own *Symbolic Shorthand System For Medicine And Physiology* using mnemonic symbols and arrows that transcended language barriers. It was generally acknowledged to be a vast improvement over the conventional Cutter and Dewey decimal systems, since it provided instant retrieval of pertinent information on any stress related subject from any publication. It was subsequently published for others to use, and went through several editions until the advent of the computer made it obsolete. He eventually accumulated a massive collection of reprints and books in a library that became world-renowned. Unfortunately, it was virtually destroyed by a fire in 1962, but since his classification system allowed him to identify each item, he immediately set about to completely restore it by writing to everyone he

knew asking them to send copies of all the reprints on stress in their collections, many of which they had originally obtained from him during the course of their own research.

Few people knew of this, nor were most aware of Selye's superb skills as an experimental surgeon. In order to trace the pathways of the response to stress, it was necessary to demonstrate the role of the pituitary and adrenal by studying the effects of removal of these organs. Taking out the adrenals required only an abdominal incision and a rudimentary knowledge of anatomy, but the pituitary posed a formidable problem. In humans, removal of pituitary tumors at the time required opening the skull at a specific site, followed by five hours of painstaking surgery to go deep into the brain without damaging other vital structures. Save for Harvey Cushing and a few others, there were not many neurosurgeons who were experienced in this transcranial approach, and morbidity and mortality rates were high. Removing a rat's pituitary without harm was equally difficult, and to obtain the dozen or more hypophysectomized but otherwise healthy animals required for each experiment would have taken weeks. Selye devised a way to remove the pituitary within two minutes that was so simple and safe, all of us quickly learned how to do it on an assembly line basis.

It consisted of a rectangular block of wood with a one-inch staple partially embedded in it at the top, and a very strong rubber band encircling the bottom. To the right, we had a beaker filled with ether soaked balls of cotton, with an adjacent cage of rats to be operated on. We would put a rat in the beaker, and after it was anesthetized in a minute or two, we placed its upper teeth under the staple, pulled down on the body until the mouth was fully open, and maintained this position by snapping the rubber band over the lower portion of the body. We wore a flashlight on our forehead and used magnifying spectacles, which allowed us to see clearly into the open mouth. (See www.cdnmedhall.org/laureates/video/?mov=selye_h.mov for an illustration of this.) Once we identified where the soft palate and hard palate met, we used a dentist's drill to make a small hole in the center of this junction that clearly revealed the pituitary and its stalk. Much like a cherry on a stem, it could easily be removed. The comatose rat was then put in an empty cage on the left to recover, a new anesthetized rat was taken from the beaker and laid out the same way, and was replaced by another to be anesthetized. We rarely lost an animal, and with a little practice, most Fellows could obtain a dozen or more specimens in a half hour. Selye told me he had been visited by Harvey Cushing, who had learned of this achievement, and had shown him how to perform the procedure.

In other experiments to study the role of the liver in responses to stress, it was necessary to demonstrate how removing a portion affected the metabolism of hormones. However, this had to be done in a standardized fashion without damaging other structures to obtain meaningful results. Selye also discovered a way to accomplish this within two minutes. Since the

lobes of the rat's liver are well differentiated and readily apparent on opening the abdomen, it was simply necessary to tie a suture completely around two of them, which allowed their bloodless removal, resulting in a two-thirds partial hepatectomy that was the same for each animal. He also devised a unique technique for studying the inflammatory response to prove that hormones like cortisone reduced inflammation, while salt retaining steroids from the adrenal cortex had the opposite effect. This was much more complicated, since it required the ability to quantify how the body responded to a standard irritant. It was also necessary to accurately measure the two components of inflammation, the prompt production of fluid and the slower response of cellular tissue proliferation.

He solved this in an ingenious fashion, by shaving the skin on the back of a rat, and then injecting air, so that a transparent sac resulted. Various irritants could then be injected and the amount of inflammatory fluid that was produced could be visualized and quantified on a daily basis by merely illuminating the sac with a flashlight. The effects of stress or injecting various steroids on fluid production were easily demonstrated, and the tissue response could be assessed by microscopic measurements of the sac wall thickness. This "granuloma pouch" technique was so simple and useful, that one could only wonder why it had not been previously thought of.

Life At Selye's Institute Of Experimental Medicine And Surgery In 1951

When I was at the Institute, **Selye's average workday was 10 to 14 hours, including weekends and holidays**. He habitually rose around 5:30, took a dip in the small pool in the basement of his house across from the McGill campus, and then rode his bike several miles to work. He was usually the first to arrive and the last to leave. On sunny days, he often put aside an hour or so after lunch to "take a nap in Miami". This was not Florida, but rather a solarium on the roof where he had the glass ceiling replaced with quartz, so that he could work on his tan during the winter. His office was a true inner sanctum, guarded by an anteroom of protective secretaries and librarians. We had to schedule an appointment with these sentries if we wished to speak with him. There was a prominent green and red light over both sides of his office door. When the red light was on, which was not infrequent, he was not to be disturbed by anyone. A green light indicated that he could now receive messages that had accumulated and important incoming telephone calls. Our conferences were conducted in French and English, which was sometimes a problem for those who primarily spoke German, Italian, Greek, Spanish, or Slavish. Selye would translate the discussion into any of these languages for Fellows requesting this, and convey their unintelligible comments to the group in French and English.

For some reason, I enjoyed a somewhat special relationship with him right from the start, possibly because he knew that I had a Master's degree in English literature and had taught English in college before entering

medical school. Although his command of the language was superb, he was still struggling with the confusion about what "stress" really signified, and was concerned about the possible connotations of other words or expressions that might have eluded him. Since most of his publications were now in English, he wanted to make absolutely certain they were perfect, and that he had not overlooked anything. I proofed several of his papers during my Fellowship and was occasionally asked to critique other manuscripts after I left to resume my medical studies.

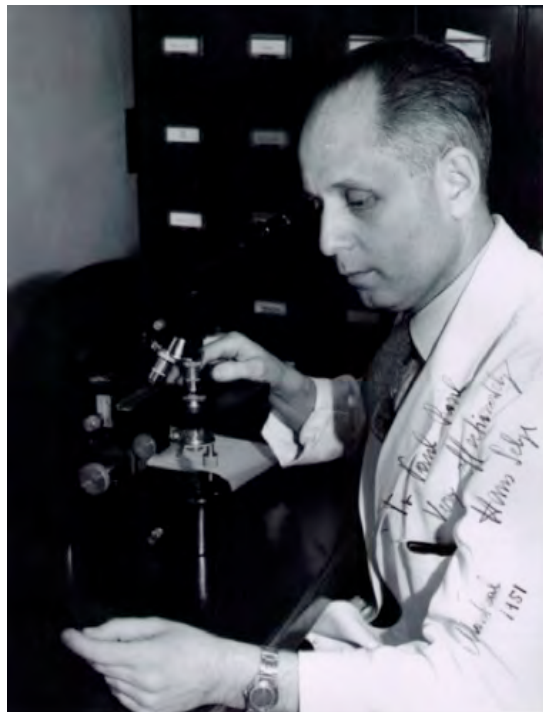
He was extremely generous, inviting me to co-author the lead Chapter "Integration of Endocrinology" for the AMA's textbook of *Glandular Physiology and Therapy* that consisted of contributions from 32 leading authorities on various endocrine disorders. He had given a presentation for The New York Academy of Medicine in 1951, entitled "The Renaissance in Endocrinology", which it wanted to publish. However, this was an extemporaneous lecture, and since it was due in a few days, he asked me to write something up from a few notes he kept and to add anything I deemed appropriate. As noted on page 13, he insisted that I be listed as a full co-author, explaining to the Academy that a major portion of this version of his lecture had been my contribution. Selye's stamina, energy and curiosity were amazing. He wrote 39 books and more than 1,700 articles on various aspects of stress and was active up until he died in 1982 at the age of 75. Some credit his success to luck, especially the serendipitous ready availability of a bottle of formaldehyde on his laboratory table at McGill in 1935. From my perspective, he illustrates Pasteur's statement that **"Chance favors the prepared mind"**, as well as Dr. Armand Hammer's observation that **"When I work fourteen hours a day, seven days a week, I get lucky."** A subsequent Newsletter will be devoted to the significance of Selye's clinical and other achievements, including the AIS – so stay tuned!

Paul J. Rosch, MD, FACP
Editor-in-Chief

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Selye pouring some champagne for us to celebrate the completion of his *1951 First Annual Report on Stress*



Autographed photo on completing my Fellowship.

Selye's magnum opus, *STRESS*, published in 1950, was a massive tome with over 1,000 pages, more than 5,000 references and numerous illustrations and diagrams that immediately stimulated thousands of articles in scientific journals throughout the world. In order to remain current, he decided to include these in an *Annual Report On Stress*, the first of which was published in 1951. It was dedicated to Fellows who were there at the time, and as noted below, I was the only one from the U.S.A. Roger Guillemin, who received the Nobel Prize a quarter of a century later, whose office was right next to mine and I are among the very few of this group that are still with us.



Ce livre est dédié à ...

Vincent W. Adamkiewicz, (Bristol, England)
 Niall Carey, (Dublin, Eire)
 Nicanor Carmona, (Lima, Peru)
 Paris Constantinides, (Αθήνας, Ελλάδα)
 Lucien Coutu, (Montréal, Canada)
 Franco Dordoni, (Roma, Italia)
 Pierre Ducommun, (Genève, Suisse)
 Didier, Dufour, (Montréal, Canada)
 Claude Fortier, (Montréal, Canada)
 Roméo de Grandpré, (Montréal, Canada)
 Roger Guillemin, (Lyon, France)
 Rudolph Hoene, (Frankfurt, Deutschland)
 Alexander Horava, (Praha, Československo)
 Bernard Jacot, (Lausanne, Suisse)
 Gaétan Jasmin, (Montréal, Canada)
 Jacques Leduc, (Montréal, Canada)
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 Perry Riet-Correa, (Porto Alegre, Brazil)
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 Paul Rosch, (Albany, N.Y., U.S.A.)
 Ernesto Salgado, (Madrid, España)
 Floyd R. Skelton, (London, Canada)
 Paola S. Timiras, (Roma, Italia)
 Sergio Yrarrazaval, (Santiago, Chile)

*... et cet exemplaire
 particulièrement au*

Hans Selye

Ce groupe enthousiaste de jeunes chercheurs qui, par dessus les frontières de leurs langues et de leurs cultures, de leurs philosophies et de leurs champs d'intérêt scientifique, ont su s'entr'aider à l'Institut de Médecine et de Chirurgie expérimentales de l'Université de Montréal, pour étudier le STRESS qui les y réunissait tous,

1950-1951

HANS SELYE, M.D., Ph.D., D.Sc., F.R.S.C., AND PAUL J. ROCH, M.D.

1

Integration of Endocrinology

INTRODUCTION

The title of this chapter might well have been "The Integrative Action of the Endocrine System," for an integration of endocrinology in itself will serve only to demonstrate more clearly the true homeostatic function of the humoral medium. The ability of man to respond and adapt successfully to his changing environment is made possible mainly by the successful co-ordinative activities of the two great integrating mechanisms, the nervous and endocrine systems.

The action of the nervous system in this respect has been the subject of intense investigation and research since the beginning of the twentieth century when Sherrington's magnum opus on this subject was published.¹ As a result, neuronal interrelationships and the function of various integrative portions of the central nervous system, such as the hypothalamus, cerebellum, basal ganglia and Area 4-8, have been clarified. A fundamental knowledge of hormonal interdependences, humoral and correlative relationships with the "nervous interface" has been slower in evolving, most of the progress having been made only in the past two or three decades.

The purpose of this chapter is to demonstrate the homeostatic nature of physiologic, hormonal interactions and to discuss those factors which elicit and condition this endocrine equilibrium. The scope of this review precludes the possibility of entering

into a detailed discussion of the function or mechanism of action of all the hormones. Perhaps an appreciation of the intricate nature of humoral balance is best obtained by observing individual instances illustrating the modus operandi of the endocrine system. Numerous examples present themselves, and the problem is one of selection, for each has its merits. Fortunately, therefore, hormonal interactions in carbohydrate metabolism and in the menstrual cycle have been chosen for initial examination. A survey of the former will disclose the manifold agencies through which hormones may exert their influences; a review of the latter perhaps will help to reveal more clearly the nature, necessity and efficacy of the delicate system of checks and counterchecks which characterizes the endocrine regulation of metabolism. A third chapter will be devoted to the endocrine interrelations during stress, a subject which has been the central research problem of our group for many years.

HORMONAL INFLUENCES IN THE REGULATION OF CARBOHYDRATE METABOLISM

The ultimate end of all endocrine activity, with regard to any aspect of metabolism, is to maintain the constancy of the "milieu intérieur," or more properly, to adjust the internal environment to the needs of the organism. Inasmuch as the level of blood sugar is one of the most important and most variable factors in the body's re-

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The above is the first page of the first chapter of the American Medical Association's textbook *Glandular Physiology and Therapy* that Selye invited me to co-author. He also asked me to conclude this by constructing a full-page color diagram showing all the endocrine glands and how they interacted. The contributors included over thirty leading authorities on various endocrine disorders. This book took almost four years to publish in order to insure that it was up to date. Selye was particularly pleased that our chapter required no changes.

Table of Contents of the 1951 New York Academy of Sciences *Lectures To The Laity* series. Selye's extemporaneous presentation had been based on a few scribbled notes that he gave me along with a request to write something that would be suitable for publication. When a proof was submitted for approval, he insisted that I be listed as co-author and explained that this version was largely my contribution. Although obviously undeserved, it was still quite an honor to be included with these celebrities.



Volume VII, *Tumors Of The Ovary*, from Selye's *Encyclopedia of Endocrinology* actually required two books. The first contained clinical descriptions, case reports, photographs of patients, X-rays, and numerous gross and microscopic illustrations of every known benign, malignant or cystic tumor of the ovary. It was "*Gratefully Dedicated to My Wife, The Motion Picture Industry and The New Yorker Magazine, without whose refreshing influence the boredom of this venture could not have been endured.*" The cartoon above from *The New Yorker Magazine* was the frontispiece for the second book, which consisted of over 18,000 references in eight different languages that had been cited in the first book. It was necessary to have two books for Volume VII since each was the size of a metropolitan telephone directory, and a single volume would have been too heavy and unwieldy.