Chapter 23
Hans Selye and the Birth of the Stress Concept

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This volume has been dedicated to assist the reader in developing greater proficiency in the treatment of the human stress response. Such a proficiency must be based upon a foundation of increased phenomenological understanding; more specifically, clinical proficiency is based upon an understanding of the phenomenology of the human stress response. Chapters 1–7 have provided the reader with a scientifically accurate yet clinically relevant introduction to the phenomenology of the stress response and its clinical implications and manifestations. But no review of phenomenology would be complete without a historical review. Virtually every chapter of this volume is replete with important historical references. Yet the authors decided to offer a final, rather unique contribution to this volume. Most of what we know about stress is attributable to one man—Hans Selye. While not always correct, Selye is nevertheless the father of the science of human stress. What drove the scientific investigations of human stress was not only the personality of the man but also his brilliance. We offer this chapter as a means of understanding the "background" of the nature and treatment of the human stress response.

For those who knew him intimately, Hans Selye would easily qualify for the *Reader's Digest*'s "Most Unforgettable Character I Ever Met" designation. However, few individuals, especially those in the scientific community, ever enjoyed that privilege because of his apparently aloof attitude. His father Hugo was a surgeon in the Imperial Austro-Hungarian Army, and it was possibly his early upbringing that resulted in his stiff, authoritarian, Prussian demeanor, which many interpreted as an air of arrogance. Born in 1907 in Komarom, a small town that at the time was in the Hungarian part of the Empire, midway between Vienna and Budapest, he attended school at a Benedictine monastery. Since his family had produced four generations of physicians, Selye

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entered the German Medical School in Prague at the age of 17 and later earned a doctorate in organic chemistry.

In medical school, Selye noted that patients suffering from very different diseases often exhibited identical signs and symptoms in the very early stages of their illness. All had low grade fevers, feelings of malaise, fatigue, generalized aching, and "they just looked sick." Excited about the possibility of studying the biochemical changes and mechanisms that might be responsible for these common findings and possibly lead to some treatment or form of relief,

Selye made an appointment to speak to the Chairman of the Department of Physiology to ask if he could study in the laboratory on weekends or in his free time after school. This individual's full name, including titles, was Hofrat Professor Doktor Armin Tschermak Edler (Nobleman) von Sysenegg. Since that was quite a mouthful, it was agreed that his highest title should be used; he, therefore expected to be addressed as "Herr Hofrat" (Counsel to the Imperial Court). Selye, who was 19 at the time and unaware of this, innocently called him "Herr Professor."

Apparently, that was the only part of his enthusiastic presentation that sank in, because when he had finished, the only response was "Well, if you are that chummy, why don't you just call me by my first name, Armin." Even after his profuse apologies, Selye's request was rejected as being so childish that it was not 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 and graduated first in his class.

Because of his obvious talent, Selye received a Rockefeller scholarship to study at Johns Hopkins University. 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 of his $150 per month stipend. Selye subsisted on mostly canned foods and often referred to this as his "sardine period," since a large tin was a bargain at 10 cents, and he ate sardines daily for months. He was warmly accepted by the other postdoctoral students, and well-meaning faculty wives, who were sorry for "the poor lonely foreign students," constantly arranged parties and social events so that the students could meet people. Although he spoke English fairly well, Selye quickly realized that Americans had their own lingo. On one occasion at a party, when he met a very attractive daughter of a prominent professor, Selye asked if they could meet again to go to a movie or dinner, and he offered to walk her home. Her response was "Yes, but would you give me a ring first?" Selye was petrified, thinking that she meant an engagement ring; he had heard many stories of the strict enforcement of "breach of promise" laws in the USA. When he congratulated another girl on her beautiful complexion by saying that her "hide" was of the finest quality, she did not take the remark as a compliment. Unfortunately, there was no distinction between *hide* and *skin* in any of the several languages Selye spoke.

He also had difficulties adapting to faculty life at Johns Hopkins, having been reared in a formal, academic European environment, where the rigid class distinctions were 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 underlings and even medical students were invited. Jackets and ties were discarded, and often everyone seemed to be on a first-name basis. Unable to conceive of Professor Hofrat or his other teachers acting in such a degrading way, Selye suffered from a severe case of culture shock. He was confused, and even considered returning home, but was told by friends that Canada was more European, traditional, and sedate. After making inquiries, Selye 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, Selye quickly found out that the language spoken by the Quebeçois was quite different. He quickly adapted and 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 nationality of his own. He spoke fluent German, Hungarian, Czech, Slovak, French, and English, since each had been his national language at one time or another. Based on the personal experience, I can confirm that he was also comfortably conversant in Russian, Spanish, Italian, and Portuguese, and could understand Swedish and a few other languages, if they were spoken slowly. Whereas his first name was Austrian, his surname was Hungarian. He was looked down on and considered an Austrian when he was in Hungary, and vice versa. When the Empire collapsed in 1918, Selye became Czechoslovakian without ever moving out of his house. The Czechs and the Slovaks had many disagreements with one another, but they both detested the Austrians and Hungarians. After Selye became an international celebrity, Czechoslovakia, Austria, and Canada, all wanted 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 his home, we consumed liberal amounts of this red wine, along with the superb Hungarian goulash he loved to make.

As instructed, he had not thought anymore about the "just being sick" syndrome that intrigued him in medical school, but by a strange twist of fate, the idea resurfaced a decade later at McGill. At the time, only two types of female hormones had been identified, but Professor Collip thought there was a third, and he assigned Selye to this research. Selye 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 new ovarian hormone. However, no such effects could be demonstrated, and to add injury to insult, many of the rats became quite sick, and some died. Although there were no changes in the ovaries of breasts, all of the rats showed enlargement of the adrenals, shrinkage of the thymus and lymphoid tissues, and ulcerations in the stomach. This did not make any sense at all, and Selye searched for some explanation. One possibility was that the changes were due to some contaminant in his chemical concoction. One day, with a bottle of formaldehyde, a toxic substance used to fix tissues for microscopic study, right in front of him, he injected liberal amounts of formaldehyde into several rats on a whim, and was amazed to find that it produced identical results.

He began to wonder if other, or all, noxious substances or stimuli could also produce these same three effects, and what ensued is now history. He exposed rats not only to powerful chemicals but also to the frigid Canadian winter, by leaving them exposed on the windswept roof of the McGill medical building. He put others 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 who survived developed the same pathology 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." He avoided using the word *stress* because of previous criticisms that, in everyday English, it implied nervous strain, and he did not want to create any confusion. However, Selye did suggest the term *alarm reaction* to describe this response, since he viewed it as a generalized mobilization of the body's defensive mechanisms.

In subsequent studies, he found that the same changes could be produced by other noxious challenges and stimuli. Animal activists were not as 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, bombarding them with constant deafening noise, making them continuously swim to the point of exhaustion to avoid drowning, and subjecting them to intense psychological frustration that bordered on torture. He also showed that the pathological changes characteristics of the "Alarm Reaction" occurred not only in rats but also in mice, rabbits, dogs, cats, and all other animals subjected to such acute insults.

Selye then studied the effects of animals' longer exposure to noxious but not lethal 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." He performed numerous, detailed autopsies during the various stages of this syndrome, and observed, on gross and microscopic examination, changes identical to those seen in patients with arthritis, kidney disease, hypertension, coronary heart disease, and gastrointestinal ulcers. He suspected that perhaps "stress" might also cause these disorders in humans as well, and therefore considered them to be "Diseases of Adaptation." Actually, "Diseases of Maladaptation" would have been more appropriate. After thousands of additional experiments, Selye found that he could produce many of these disorders selectively, by sensitizing or conditioning the animals through certain dietary or hormonal manipulations, and subjecting them to different types of distressful insults.

He subsequently traced the pathways and mechanisms 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 steroids that would reduce inflammation. This explained why the adrenals were enlarged. Similarly, the stomach ulcers and lymphoid tissue shrinkage were due to the increased amounts of cortisone-like hormones. If he removed the pituitary and repeated the experiments, 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 them, or to treat the resultant diseases more effectively. These were entirely new and very radical concepts.

As a result of Pasteur's research and Koch's postulates, physicians had always 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 specific microorganisms, and so on. What Selye proposed was actually the complete reverse of this. He had 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 findings. While each of these might also have their own specific hallmarks, such as a burn, or frostbite, all nevertheless caused the same nonspecific changes in the adrenal, stomach, and lymphoid tissue he had first seen following the injection of his new ovarian hormone extract. Perhaps this also explained the curious and very common syndrome of "just being sick" that he had observed as a medical student, in the early stage of illness in patients who later went on to develop very different diseases.

He chose the word *stress* to describe this phenomenon, defining it as "the nonspecific response of the body to any demand for change." It turned out to be an unhappy decision that would haunt him the rest of his life. The term 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 not aware that the word *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 withstand before becoming permanently deformed is referred to as its elastic limit. This ratio of stress to strain, a characteristic property of each material, is called the modulus of elasticity. Its value is high for rigid materials, such as steel, and much lower for flexible metals, such as tin. Selye complained several times 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 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 asked to give an address at the prestigious College de France, the academicians responsible for maintaining the purity of the French language struggled with this problem for several days and subsequently decided that a new word would have to be created. Apparently, the male chauvinists prevailed, and *le stress* was born, quickly followed by *el stress, il stress, lo stress,* and *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 form among these latter languages. 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, the 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 the ultimate result of this interaction. Thus, an unreasonable and overdemanding boss might give you heartburn or stomach pain, which eventually resulted in an ulcer. For some people, stress was the bad boss, while others used stress to describe either their "agita" or their ulcer.

Because it was clear that most people viewed stress as some unpleasant threat, Selye 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 laboratory research to apply to humans. In helping to prepare the *First Annual Report on Stress* in 1951, I included the comments of one critic, who, using verbatim citations from Selye's own writings, concluded that "stress, in addition to being itself, was also the cause of itself, and the result of itself."

I first met Selye in 1949, when he was writing his monumental tome, *Stress.* He was already regarded internationally as one of the world's leading authorities on endocrinology, steroid chemistry, experimental surgery, and pathology. He had singly authored one of the first textbooks of endocrinology, as well as a 27-volume *Encyclopedia of Endocrinology,* covering every aspect of this subject. Selye did everything on a grandiose scale. *Stress,* which was published in 1950, was a huge book of over 1,000 pages, containing more than 5,000 references. However, it paled in comparison to his *Encyclopedia of Endocrinology,* where each of the proposed 27 volumes was the size of a metropolitan telephone directory.

A voracious reader, he consumed everything from the most technical and esoteric journals, in eight languages, to popular magazines and pulp fiction, and he did this with lightning speed. He read as fast as most people could skim, and he could skim a book in almost the time it took to turn pages. However, he seemed to retain as much from skimming a page as most of us would from reading it, because of an amazing photographic memory. He could sometimes 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 Police Gazette,* the forerunner of *The National Enquirer.* He almost compulsively retained copies of every article in any scientific or lay publication remotely dealing with stress, but it did not 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, repeating this process over and over, which resulted in a never-ending chain of requests for reprints in different languages from all over the world.

The problem lay 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 publications. Subsequently published for others to use, it went through several editions, until the advent of the computer made it obsolete. Selye eventually amassed a monstrous 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, Selye immediately set about completely restoring 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 research!

Few people were 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 glands 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 very specific site, followed by 5 h of painstaking surgery to go deep into the brain without damaging other important structures. Outside of Harvey Cushing and a few others, few neurosurgeons were experienced in this trans-cranial operative procedure, and morbidity and mortality rates were high. Removing a rat's pituitary without harming the animal was not much easier, and to obtain the dozen or more hypophysectomized but otherwise healthy animals required for each experiment would have taken weeks. Selye found a way to remove the pituitary within 2 min, and it was so simple and safe that we all quickly learned to do it on an assembly-line basis. It consisted of a rectangular block of wood with a 1-in. staple partially embedded in it at the top, and a very heavy rubber band encircling the bottom. To the right, we had a beaker filled with ether-soaked balls of cotton, next to which was a cage of rats to be operated on. We would put a rat in the beaker, and after it was anesthetized, which took a minute or two, we placed its upper teeth under the staple and pulled down on the body until the mouth was fully open, maintaining this position by snapping the rubber band over the lower portion of the body or tail. We wore flashlights on our foreheads and used magnifying spectacles, which allowed us to see clearly into the open mouth. Once we had identified where the soft palate met the hard palate, we used a dentist's drill to make a small hole in the center of this junction, which clearly revealed the pituitary and its stalk, and much like a little cherry on a stem, it could easily be removed. The comatose rat was then put in an empty cage on the left to wake up, a new anesthetized rat was taken from the beaker and laid out the same way, then replaced by another to be anesthetized. We hardly ever lost an animal, and with a little practice, most of us could obtain two dozen specimens in a half hour. Selye told me he was visited by Harvey Cushing, who had heard about this remarkable achievement, and also taught him how to perform the procedure.

In later experiments, it was necessary to study the effects of removal of part of the liver on the metabolism of hormones and responses to stress, but this had to be done in some standardized fashion, and without damaging other structures. Selye discovered a way to also accomplish this in less than 2 min. Since the lobes of the 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. Selye also devised a unique technique for studying the inflammatory response in order to prove that ACTH and glucocorticoids reduced inflammation, while STH (growth hormone) and mineralocorticoids promoted it. This was much more complicated, since it required the ability to quantify the irritant and the body's response to allow accurate measurements and to ensure consistency. There was also the need to separate the two major components of inflammation, the cellular reaction, with its resultant tissue proliferation, and the production of inflammatory fluid. 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 trans-illuminating the sac with a flashlight. The effects of stress or of injecting various steroids were easily demonstrated, and the tissue response could be measured by studying the thickness of the wall of the sac under the microscope. This granuloma pouch technique was so simple and useful that we could only wonder why no one had thought of it before.

When I was at the Institute, Selye's average work day was 10–14 h, including weekends and holidays. He habitually rose around 5:30 A.M., took a dip in the small pool in the basement of his house, which was 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 had the glass ceiling replaced with quartz, so that he could work on his tan during the winter. As a result of his research on the experimental production of myocardial necrosis and the benefits achieved by Sodi Pallares's polarizing solution containing potassium in acute heart attacks, he filled all his salt shakers with potassium chloride. It tasted horrible, but he was convinced it would protect his heart and reduce risk for hypertension and stroke. Recent research findings have shown that he was absolutely correct. He regularly took garlic pills, he told me, not only because of their health benefits but also because his breath discouraged prolonged, close conversations, especially with strangers who frequently cornered him during his travels, and he used this effectively.

Selye's office was a real inner sanctum, guarded by an anteroom of protective secretaries and librarians. We had to make an appointment with these watchdogs if we wished to speak with him. There was a prominent green and a red light over both sides of his entry door. When the red light was on, which was not infrequently, he was absolutely not to be disturbed by anyone, including these wardens. A green light indicated that he could now be approached with messages that had accumulated, or important incoming telephone calls. For some reason, I enjoyed a somewhat

special relationship with him right from the start, possibly because he knew that I had been an English teacher before entering medical school. Although his command of the language was superb, he was still struggling with the confusion surrounding what "stress" really signified, and was concerned about the possible connotations of other words or expressions that might have escaped him. Since most of his publications were now in English, he wanted to make absolutely certain that they were letter perfect, and that he had not overlooked anything.

He was extremely generous, inviting me to coauthor the lead Chapter "Integration of Endocrinology" for the American Medical Association's *Textbook of Glandular Physiology and Therapy,* which included contributions from 32 leading authorities on various hormonal disorders. He had given a presentation to the New York Academy of Medicine in 1951, which they wanted to publish. However, it had been an extemporaneous speech, so he asked me to write something up from his notes and to add anything that I deemed appropriate, or that he might have neglected. When a preprint was submitted for his approval, he again insisted that I be listed as a full coauthor, explaining to the Academy that a major portion of this final version had been my contribution.

Selye was not well received by his peers, who considered him arrogant and aloof. Many also resented that they could not evaluate much of his research without purchasing expensive publications from Acta Inc., which Selye owned completely. Selye explained to me that he had established this company in self-defense to speed up publication of *Stress* and subsequent works, rather than for any financial gain. Conventional medical publishing houses often took up to a year to get a book into circulation, and it was difficult to make any changes once the galleys had been set. However, since he had complete control of Acta, located a few miles away, he could readily insert any late-breaking research to ensure accuracy and timeliness. He had quarrels and feuds with prominent endocrinologists such as Dwight Ingle and George Engel, and although he was not liked, he was respected. Even many of his adversaries felt that he should have shared in the Nobel Prize given to Kendall and Hench. I had arranged for him to give a talk at Johns Hopkins when I was involved in the Endocrine Clinic with giants such as John Eager Howard, Lawson Wilkins, Harry Klinefelter, and Sam Asper. Although he was well received, I was surprised at the somewhat antagonistic attitude of these good friends, who also viewed him as somewhat pompous.

We continued to keep in close contact while I was at Johns Hopkins, and later, when I headed the Endocrine Section at Walter Reed Army Medical Center. He periodically commissioned me to write articles or review his own, even after I entered private practice. Over the next two decades, he became an international celebrity. Because of several books written for the public, which were high on the best-seller lists for months, he was in wide demand as a speaker all over the world, attracting large audiences and commanding huge fees. He had numerous requests for consultations but, to the best of my knowledge, never saw a patient. After I entered private practice, he regularly referred many patients to me, including several very famous individuals. He later developed a rare and usually fatal malignancy, and attributed his recovery to his strong desire to continue his research. He asked me to

contribute a presentation on Stress and Cancer to a Symposium that his Institute conducted with Sloan-Kettering in 1978, which led to my present interest in this subject. He was adamant about my helping him establish the American Institute of Stress, and later assuming its Presidency, as well as serving on the Board of his International Institute of Stress.

In the final analysis, much of what he believed and proposed was not correct. However, his real legacy can be summed up by what he often reminded me, namely, that theories do not have to be correct—only facts do. He pointed out that many theories are of value simply because of their heuristic benefit, in that they encourage others to discover new facts that then lead to better theories. Hans Selye's propaedeutic contributions to our understanding of stress and its relationship to health and illness vividly illustrate this maxim.