HEALTH AND STRESS

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The American Institute of Stress

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ON THE ORIGINS AND THE EVOLUTION OF "STRESS"

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It's difficult to get through the day without running into some reference to "stress" on television, in newspapers and periodicals, and especially casual conversation. Why all the fuss? After all, stress has been around since Adam and Eve were in the Garden of Eden.

Is it because there is **more stress today? Is contemporary stress somehow different or more dangerous?** Or is it due to the fact that **scientific studies over the past several decades have confirmed anecdotal reports of the significant role of stress in different diseases and delineated the diverse mechanisms of action** that may be involved? It seems likely that all of these influences have been contributing factors.

In addition, the recent increased interest in "alternative" and "complementary" medicine approaches that emphasize mind/body relationships has led to a variety of stress reduction techniques for the treatment of disorders and symptoms that are believed to be stress-related.

Despite its popularity, stress is not a very useful term because it has become an idiomatic expression that is difficult to define. In its vernacular use, stress often signifies very different things to different people. **If you can't define stress, you obviously can't measure it or conduct research studies on its effects that would have any validity.** Numerous suggestions and proposals have been offered over the past four decades but there is sill no objective definition of stress that satisfies the standards required by the scientific community.

Our physical responses to stress also differ. Some people blush, others get pale, have palpitations, sweaty palms, dermatologic or gastrointestinal symptoms. In addition, things that are distressful for some may be pleasurable for others, as readily illustrated by observing passengers on a steep roller coaster ride. Some in the back are slouched down, eyes shut; jaws clenched and white knuckled as they clutch the retaining bar. They can't wait for the ride in the torture chamber to end so they can get back on solid ground and get away. But up front are

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the wide-eyed thrill seekers, screaming with delight at every steep plunge, who race to get on the very next ride. In between, you might find a few riders with an air of nonchalance that almost seems to border on boredom. Was the roller coaster ride stressful? How much and for whom? How **Hans Selye got us into this stress-mess** state is a fascinating story.

Claude Bernard And The Milieu Intérieur

Selye's theories had their origins in the research of Claude Bernard, often referred to as "The Father of Physiology". Bernard had studied to be a surgeon but was disturbed about the lack of any rationale to explain how mechanisms in the body interacted to achieve specific goals. In 1846, he noted that the urine of hungry rabbits was clear instead of its usual turbid appearance and found that it was also acidic rather than alkaline. Since rabbits are herbivorous and these hungry rabbits had not been fed for days, Bernard suspected that fuel for energy had come from their own fat and protein stores that were being broken down. Sure enough, after he fed them grass, the urine returned to its normal alkaline turbidity.

In contrast, the urine of healthy human meat eaters is usually clear and acidic. He experimented on himself by subsisting only on vegetables, salad and fruit and noted that within 24 to 36 hours, his normally acid and clear urine had turned alkaline and cloudy. What caused this and what purpose did it serve? He subsequently starved some rabbits and then fed them meat and observed during surgery that the usual clear secretion from the pancreas into the gut had now become milky.

Bernard concluded that the pancreas somehow was able to emulsify fats under these circumstances so that they could be better absorbed to provide fuel when needed. He subsequently discovered a white starchy material in the liver called glycogen that was built up from sugar and seemed to serve as a storage reservoir for carbohydrates. He demonstrated how the liver broke down glycogen to secrete glucose directly into the blood stream in response to emergency situations or when it was needed to maintain blood sugar concentrations within normal limits. He deduced that the liver, pancreas and probably other organs somehow acted in concert to maintain normalcy. He also distinguished the ductless (endocrine) glands from those with ducts (exocrine) and originated the term "internal secretion", which later became hormone from the Greek *hormaein*, to spur on or set in motion.

Bernard investigated the autonomic nervous system and discovered how the vasomotor nerves regulated blood flow by controlling the dilation and constriction of vessels depending on the body's needs. In cold temperatures the blood vessels of the skin constricted in order to conserve heat, while in hot weather they dilated to dissipate excess heat so that body temperature would be kept constant. He wrote "All the vital mechanisms, however buried they may be, have only one object: that of preserving constant the conditions of life in the inner environment (milieu intérieur)".

Like the glycogenic functions of the liver and the pancreatic response to dietary changes, these automatic alterations in blood vessel caliber illustrated how the body tried to maintain the stability of the internal environment by responding to any stimulus that attempted to change things. He concluded that **"It is a fixity of the *milieu intérieur* which is the condition of free and independent life"**. Bernard subsequently accepted the Chair of Physiology the Sorbonne had created for him and later became President of the prestigious Collège de France. He was so highly respected, that upon his death in 1878, he was given a public funeral, the first for any French scientist.

Walter Cannon And Homeostasis

Bernard's major contribution was his concept of an internal environment (*milieu intérieur*) and conclusion that health and life itself depended on the ability to maintain its constancy whenever the status quo was threatened. This made a lasting impression on Selye, who always credited Bernard for inspiring him. He established an annual Claude Bernard Lecture and Medal for distinguished stress researchers at his Institute of Experimental Medicine and Surgery at the University of Montreal, which he established after he left McGill. His other hero was Walter Bradford Cannon.

Cannon also had a deep respect for Bernard and some fifty years later, **referred to his "fixity of the *milieu intérieur*" as the "steady state". He also coined the term "homeostasis"** to describe the numerous balancing mechanisms necessary to maintain it, from the Greek *homoios*, meaning similar, and *stasis*, the ability to stay the same, or static. His interest in Bernard actually stemmed from the 1895 discovery of Roentgen or X-Rays that could be used to visualize abnormalities inside the body. By 1897, Cannon had found that he could use bismuth and barium mixtures to trace how they passed through the gullet of geese and other animals because they were opaque. He developed the use of barium in his laboratory at Harvard for diagnostic x-ray studies of the human gastrointestinal tract by incorporating it into a liquid or semi solid concoction and following its passage through the gut with a fluoroscope or periodic X-Ray films. This allowed him to readily demonstrate lesions, especially if they caused obstruction, and this same technique is still used to perform a GI series or barium enema.

However, Cannon's major interest was in investigating the peristaltic motor activities responsible for progressively propelling food through the gut. Under normal circumstances, this was a smooth and rhythmic series of contractions that caused various valves to open to let the bolus pass and then close. He also noted that when his experimental animals were very hungry, these peristaltic waves increased in frequency and amplitude.

On occasion, this movement can create noises loud enough for others to hear, prompting them or you to say your stomach is "growling" because you are hungry. Cannon had also observed that if one of his experimental cats became frightened for some reason, peristalsis would immediately stop. It was this serendipitous discovery that led him to explore the physical effects of different emotions on the gut. His further investigations revealed that the responses during fright were due to stimulation of the sympathetic nervous system and the secretion of a hormone he called "sympathin", as well as an outpouring of adrenine (adrenaline) from the adrenal medulla. By 1915, Cannon had concluded that the greatest stimulation occurred during extreme hunger, thirst, fear, rage or sexual activity. These precipitated an automatic and immediate cascade of integrated responses throughout the body that prepared the organism for "fight or flight".

These myriad reactions had been exquisitely honed over the millions of years of man's evolution as life preserving measures: dilatation of the pupils improved vision; increased heart rate and blood pressure delivered more blood to the brain to improve decision making; blood clotted more quickly to reduce loss from lacerations or internal bleeding; blood sugar rose to provide more fuel for energy from the breakdown of body carbohydrate stores; muscle tension increased; the flow of blood was shunted from the gut, where it was not immediately needed for digestive purposes, to the large muscles of the arms and legs to provide more strength in combat or speed of locomotion away from a scene of potential peril.

Cannon summarized the mechanisms that maintain the stability of heart rate, blood pressure, temperature, sugar, protein, fat, calcium, and oxygen concentrations in the blood needed to maintain life under normal and emergency conditions in his 1932 *The Wisdom of the Body*. He believed that any seemingly useless responses to stress that people experienced, such as gooseflesh, the hairs on the back of your neck "standing up" or diarrhea, could be shown to have served some useful purpose at some time during the course of our evolution.

Hans Selye And "They Just Looked Sick"

Exactly what is stress? Although the word has been used in the English language for over four centuries, its current meaning dates back only six decades, when it was essentially "coined" by the brilliant Canadian investigator Hans Selye. Selye, who had entered the German Medical School in Prague at the age of 17, was intrigued that **patients suffering from very different diseases often exhibited identical signs and symptoms in the first few 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 might be responsible for these common findings since this could possibly lead to some treatment or form of relief and asked if he could study this in the laboratory on weekends or free time. He was told that his request was so inane it was not worth discussing. If a person is sick, he obviously looks sick, just as if he is fat, he looks fat, and that he should spend his free time studying for his exams.

Selye graduated first in his class, later earned a doctorate in organic chemistry, and because of his obvious talent, received a Rockefeller scholarship in 1931 to study at Johns Hopkins. He had difficulty in adapting to its informal academic attitude and transferred to McGill Medical School in Canada, where things were more European and he could work under the renowned biochemist J.B. Collip. At the time, only two ovarian hormones had been identified, but Professor Collip thought there was a third, and assigned Selye to this research. He was sent to the slaughterhouses with a large bucket and told to retrieve as many cow ovaries as possible. Collip then reduced these 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. Even worse, most of the rats injected with Collip's new extract became very sick, and some died.

Selye was a meticulous investigator and although autopsy revealed no microscopic changes in the ovaries or breasts, he observed that all of the rats showed ulcerations in the stomach, enlargement of the adrenals, and shrinkage of the thymus and lymphoid tissues. This didn't make any sense at all, and the only explanation he could think of was that these abnormalities were due to some contaminant in Collip's chemical concoction. There was a bottle of formaldehyde, a toxic substance used to fix tissues for microscopic study right in front of him. On a whim, he injected liberal amounts of the solution into several rats, and was amazed to find that this produced results identical to those observed with Collip's new extract.

Selye decide to see what would happen if he injected other toxic chemicals. He found that although they had other effects on different organs and structures, there were always the characteristic changes in the stomach, adrenals, thymus and lymphoid tissues. He wondered whether a noxious physical stimulus would produce these same changes. He exposed rats to the frigid Canadian winter by leaving them on the wind swept roof of the McGill medical building. He put them in a revolving barrel-like treadmill driven by an electric motor, so that they had to constantly run to stay upright. Others were dumped into a water barrel so they had to keep swimming to prevent drowning. Sure enough, all that survived after a day or so of this agonizing physical torment showed the same pathology produced with Collip's extract and formaldehyde.

He subsequently demonstrated that severe emotional threats could also do this in experiments that would be impossible to perform today. He sewed back the eyelids of immobilized animals so they would constantly be looking into a very bright light. Others were subjected to continuous deafening and irritating noise, or intense psychological frustration that also bordered on torture. The results were identical. Selye viewed this and the very early symptoms in sick patients he had observed as a medical student as **a nonspecific response to what he considered to be "biologic stress".**

Is It "Strain", *Le Stress* or *La Stresse*?

In 1936, Selye submitted his findings to the Editor of *Nature* who agreed to publish a 176-line letter if he omitted the word stress, and with good reason. At the time, stress was commonly used as a variant of "distress" and most often referred to "nervous strain". Selye also did not recognize 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. Hooke's Law (1658) stated that the magnitude of an external force (**stress**) would produce a proportional amount of deformation (**strain**) in a malleable metal. The ratio of stress to strain is a characteristic property of all material

called the modulus of elasticity. Its value is high for rigid materials like steel and much lower for flexible metals like tin.

Therefore, "strain" would have been preferable, and Selye complained to me on several occasions that had he been aware of this, he would have gone down in history as **the father of the "Strain" concept**. This also created confusion when his research had to be translated into other languages. He was invited in 1946 to give a presentation at the prestigious Collège de France where the great Claude Bernard had served as President. The academicians responsible for maintaining the purity of the French language were unable to find a suitable word or phrase to convey Selye's concept of stress, since he was really describing strain. They struggled with this for several days, and eventually decided that a new word would have to be created. The male chauvinists prevailed and *le stress* was chosen over *la stresse*.

This was 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 few words you will still see preserved extant in languages that do not use the Latin alphabet. Hippocrates had written that disease was not only *pathos* (suffering), but also *ponos*, (toil), as the body fought to restore things to normal. While *ponos* might have sufficed, the Greeks also adopted stress.

Is Stress Cause, Effect Or Both?

Back home, there were other difficulties as "stress" became increasingly incorporated into everyday speech and eventually a popular buzzword. However, it 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 over demanding boss might give you heartburn or stomach pain that eventually resulted in a peptic ulcer. For some, stress was the bad boss while others used stress to describe their "agita", stomach pain or their ulcer.

Even Selye had difficulties when he tried to extrapolate his laboratory research to humans. In helping him to prepare his *1951 First Annual Report On Stress*, I included the comments of one physician that had appeared in the *British Medical Journal*. Using verbatim citations from Selye's own writings, **he had reached the conclusion that "Stress, in addition to being itself, was also the cause of itself, and the result of itself."**

Because it was apparent that most people viewed stress as some unpleasant threat, **he had to create a new word, "stressor" to distinguish stimulus from response**. There were other problems. All of Selye's experiments had been conducted with laboratory animals and only focused on the damaging effects of stress. When it came to human beings, it was apparent that stress was not always necessarily harmful. **Increased stress results in increased productivity** up to a point, and this differs for each of us. It is only when we exceed this optimal level that stress starts to become damaging.

Nor was stress necessarily a synonym for something bad. Winning a race or election may be just as stressful as losing, and is often more so. A very passionate kiss and contemplating what might follow could be described as stressful, but is hardly the same feeling you have during root canal work. Were the physiological changes associated with "good" stress different? Could "good" stress negate the effects of "bad" stress? Selye believed this was possible and later coined the term **"eustress" to refer to stress that might promote health**.

Selye's "Diseases Of Adaptation"

Selye's initial 1936 publication was entitled "A Syndrome Produced by Diverse Nocuous Agents". As indicated, the editor of *Nature* deleted any mention of stress. He also substituted "nocuous" for "noxious", which Selye had originally used, since noxious had the connotation of a personal reaction to someone or something rather than biological harm that could be seen objectively. Selye described the syndrome he observed following exposure to nocuous agents as developing in three stages.

The first occurred within 6-8 hours and included a rapid decrease in the size of thymus and lymphoid tissues, "loss of lipoids

and chromatin substance" from the adrenal cortex, the appearance of ulcerations in the stomach and erosive lesions elsewhere in the gastrointestinal tract. There could also be edema formation, disappearance of fat tissue, loss of muscular tone, fall in body temperature, pleural and peritoneal effusions and focal necrosis of the liver. In the second stage, which began 48 hours after injury, the greatly enlarged adrenals "regain their lipoid granules" and numerous basophiles appeared in the pituitary indicative of an increase in production of hormones that stimulated the adrenal and thyroid. If exposure continued for a month or more (depending on the severity of the stimulus), a third stage ensued, in which "the animals lose their resistance and succumb with symptoms similar to those seen in the first stage."

Selye viewed this first stage as a "call to arms" of the body's defenses and referred to it as the **"Alarm Reaction"**. The second represented a **"Stage of Resistance"**, during which the mobilization of these coping responses was maximized. Continued exposure to the stressor ultimately resulted in destructive damage or death in a final **"Stage of Exhaustion"**. Selye subsequently termed this tripartite response the **"General Adaptation Syndrome"**. He performed thousands of experiments using different kinds of noxious stimuli. He also varied their intensity and duration of application, and made detailed observations of his autopsy findings at different intervals following the initial exposure.

These revealed pathologic changes in the cardiovascular system, kidneys, gastrointestinal tract, soft tissue and other structures indistinguishable from those seen in patients suffering from heart attacks, stroke, peptic ulcers, rheumatoid arthritis and other disorders. He reasoned that if stress could cause this in his laboratory animals, perhaps it could contribute to these and other diseases in humans. He called these "Diseases of Adaptation", although in retrospect, we both agreed that "Diseases of Maladaptation" might have been preferable.

I first met Selye shortly after his massive tome *Stress* appeared in 1950, detailing the results of his experiments that led to the formulation of the General Adaptation Syndrome. His concept of different "Diseases of Adaptation" resulting from stress electrified the scientific community. Because of Pasteur's accomplishments 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, etc.

What Selye was proposing was actually the complete reverse of this. He had now demonstrated that very different chemical and physical challenges, as well as severe emotional threats could consistently produce identical gross and microscopic findings in certain organs and tissues, even if they were opposite. Extreme cold would cause frostbite and searing heat would result in a burn. While these were telltale specific effects that differed, both resulted in the same nonspecific findings seen with Collip's extract and other noxious agents.

In addition to his universal "Alarm Reaction" response, prolonged exposure to the stressor resulted in pathologic changes in various organs that mimicked those seen in patients with various disorders, depending on the nature and severity of the stressor, and the duration of exposure. **He subsequently learned how to consistently produce specific Diseases of Adaptation** by selecting a specific stimulus and sensitizing his experimental animals via diet or the prior administration of desoxycorticosterone and other steroids.

Is Animal Research Pertinent To People?

Although animals differ from humans in many ways, researchers have always attempted to find some clinical significance to their laboratory discoveries. Claude Bernard's greatest contribution in that regard was demonstrating how the liver could break down glycogen to provide glucose in response to emergency situations or when blood sugar levels had to be maintained within normal limits and his deduction that the liver, pancreas and possibly other organs acted in concert to maintain normalcy. Bernard was fascinated with the philosophy of science and devoted

the last section of his 1865 *Introduction to the Study of Experimental Medicine* to a discussion of the social aspects of his research, and wrote "The ideas which we will here set forth are certainly by no means new; the experimental method and experimentation were long ago introduced into the physico-chemical sciences, which owe them all to their brilliancy ... We shall therefore make no claim to philosophy. Our single aim is, and always has been, to make the well-known principles of the experimental method pervade medical science."

William Ballis, an English researcher, continued Bernard's studies on pancreatic function and the mechanisms responsible for maintaining the constancy of the *milieu intérieur* and referred to it as **"the wisdom of the body"**. Walter Cannon later adopted this for the title of his book, dedicated the French edition to Bernard and acknowledged his debt to him in the Preface. "The central idea of this book, the stability of the inner medium of the organism in higher vertebrates, is directly inspired by the precise views and deep understanding of the eminent French Physiologist Claude Bernard. This book can even be considered a tribute to his memory." Walter Cannon was also intrigued by the social implications of this concept and entitled the epilogue to **The Wisdom of the Body** "Relations of Biological and Social Homeostasis".

However, it was Hans Selye who made the giant leap from the laboratory to the clinical arena to extrapolate the biological and psychosocial implications of his animal research. However, like Bernard and Cannon, he could only theorize based on what was known at the time.

Bernard knew nothing about adrenal medullary hormones and Cannon had scant knowledge of the secretions of the adrenal cortex and pituitary other than that they were essential for life. Until the late nineteenth century, the human pituitary was thought to be a vestigial organ. The first pituitary hormone was not isolated until a year after Selye's first publication and since then, researchers have identified eight other hormones in three sections of the pituitary, many of which were not known to Selye.

Nor was he aware of a host of small peptide neurotransmitters that originate in the brain and gut. Like hormones from endocrine glands, they travel via the blood stream to exert effects far from their sites of origin that can play an important role during stress to maintain homeostasis. Selye had delineated the role of the pituitary-adrenal axis in the response to stress and searched for the origin of this stimulus, which he believed was a hypothalamic hormone. This was later clarified by Roger Guillemin, whose office was next to mine at Selye's Institute of Experimental Medicine and Surgery in 1951. Roger received a Nobel Prize 26 years later for identifying corticotrophin releasing factor as well as endorphin, and other brain peptides.

Selye was aware that new discoveries would require changing his theories, but as he often reminded me "Theories don't have to be correct, only facts do. Some theories are of heuristic value in that they encourage others to develop new facts that lead to better theories." Are there any better theories that allow us to more meaningfully define stress? Are things any clearer now than in 1936?

Let's go back to the roller coaster. What distinguished the people in the back from those up front was their sense of control over the event. Neither group had any more or less control, but their perceptions and expectations were different. Although stress is difficult to define, all our clinical and laboratory studies confirm that **the feeling of having no control is always distressful. That's what stress is really all about.**

Stress Research Is Starting To Soar South Of The Border And In South America

The Foreword to Selye's 1947 **Textbook of Endocrinology** was written by Bernardo Houssay, the great Argentinean physiologist who received a Nobel Prize the same year for his ground breaking research on the function of the anterior pituitary. I met Houssay when he came to visit Selye in 1951, shortly after the English version of his *Human*

Physiology was published. It was far and away superior to anything else, especially with respect to the endocrine system, and the contributions of Braun Menendez and other Argentinean colleagues were impressive. Selye's 1951 *First Annual Report On Stress* was dedicated to 28 researchers from all over the world who had Fellowships his Institute. Most were from Europe and Canada, I was the only one from the U.S., and can recall Nicanor Carmona (Lima, Peru), Sergio Yrarrazaval (Santiago, Chile), Jose Procopio (Rio de Janeiro, Brazil), Perry Riet-Correa (Porto Alegre, Brazil) and Juan Paullada from Mexico City. However, I have not been aware of very much interest in stress in these countries over the past few decades.

I was therefore pleasantly surprised to receive invitations to Congresses devoted to stress in Argentina and Brazil, both of which were carefully planned and very well attended. Dr. Daniel Lopez Rosetti had organized The First Argentina Congress on Stress Medicine in Buenos Aires (June 1-2) at which I gave the opening and closing presentation. I also gave the opening paper at the ISMA-Brazil Congress arranged by Dr. Ana Maria Rossi on June 12. On August 16, I will be opening a 3 day Conference in Juarez, Mexico to inaugurate an Institute being named in my honor (Instituto Internacional de Medicina del Estres Dr. Paul J. Rosch) and will be joined by my good friend Demetrio Sodi Pallares. Dr. Rosetti and Dr. Rossi were thoughtful and generous hosts and arranged for Marguerite and I to visit local attractions and enjoy fine dining. The Brazil Congress included Dick Rahe and Jim Quick as past and incoming ISMA-USA Chairs but I only have pictures of two of *The Three Caballeros* from the chiarrascura feast of meats and Gaucho show.

Dr. Rossi & Dr. Rahe

Marguerite & Dr. Rosch

Dr. Rosch's Presentation at ISMA-BR

We had to fly home the next day, but Dr. Rossi also hosted a trip to the wine country for Dick and Jim. There is not enough room for photos taken at the spectacular tango show and excellent dinner Dr. Rosetti arranged for us in Buenos Aires. Am looking forward to Mexico - so stay tuned

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