CHAPTER 10

Hans Selye, Hormones, & Stress

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INTRODUCTION

Many people who enjoy a good chicken dinner are not aware that the plumpest, most tender meat comes from roosters that were castrated when they were young. Someone probably discovered this accidentally, when they castrated a rooster to reduce its overall activity. Arnold Berthold wondered how removal of the testicles brought about these anatomical and behavioral changes. Did the testicles somehow interact with the nervous system to bring about normal development and behavior? Alternatively, maybe they produced some substance that was essential for normal development and behavior. If so, what was this substance, and how did it exert its control?

In 1848, he castrated two young roosters and transplanted their testicles into their abdominal cavities. Rather than maturing into fat, tender, and inactive capons, the birds behaved normally, defending their territories, crowing and strutting with all the vigor and enthusiasm of true roosters. Berthold autopsied these animals and found no evidence of nerve regeneration but discovered a rich network of capillaries connecting the testicles and the circulatory system. He concluded that the testicles were contributing something to the blood via this capillary network that affected rooster behavior and anatomy.

In subsequent decades, organ removal studies similar to those conducted by Berthold revealed a great diversity of chemical messengers—hormones—that are carried in the blood. Hormones are released by many glands and organs and may stimulate or inhibit the activities of sensitive tissues or organs. By the early twentieth century, a great hormones search was in full swing. In a modification of Berthold's technique, physiologists removed glands suspected of being sources of hormones, ground them up, and added solvents to extract the suspected hormones from the glands. These extracts were then injected into test animals, which were studied for anatomical, physiological, or behavioral changes. This blind trial-and-error technique sometimes led to discovery of new and important hormones and, other times, led to dead ends.

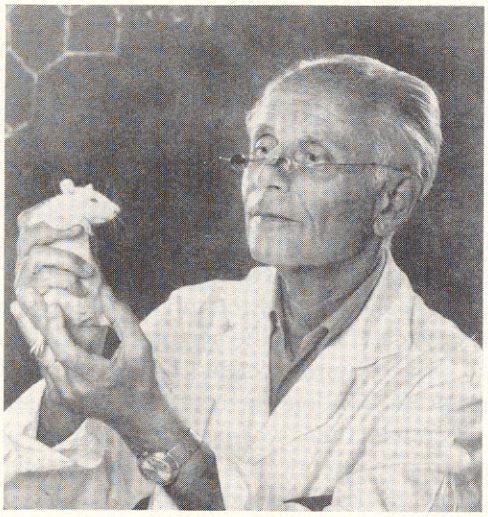

FIGURE 10.1 Hans Selye inspecting one of his many experimental subjects. *Source:* © Karsh, Ottawa.

In at least one case, an investigator did not accomplish his intended mission. Instead, Hans Selye opened up an entirely new field of inquiry only partly related to his initial experiment.

HANS SELYE

Hans Selye (Figure 10.1) entered endocrinology when the field was in its heyday. Following a long family tradition, Selye became a physician. Selye was impressed by his father's technical expertise and moved by his sense of humanity and compassion. If the patient was poor and unable to pay for a physician's services, rather than charge for the visit, Selye's father would often leave a small sum of money behind. Years later, Selye decided to forsake a clinical career in favor of a life devoted to medical research. This decision was not made lightly. Selye wrote with considerable sadness that he would never have the satisfaction of seeing the grateful eyes of a mother whose child has been saved from certain death.

Selye grew up in a multicultural family. His father was Hungarian, his mother Austrian, and his two governesses English and French. After the shifting of national boundaries following World War I, his hometown became Czechoslovakian. Thus he could boast of having six native tongues, to which he added several others during the course of his lifetime.

As a result of his dynamic personality and his ability to communicate in many languages, Selye was a very charismatic figure. He was a brilliant lecturer who could draw two different pictures on the blackboard using both hands simultaneously while carrying on a conversation about what both hands were doing. His powers of persuasion were unparalleled, in part because he was fluent in so many languages and in part because he was a prolific writer, authoring 38 books and approximately 1,700 articles over the course of his lifetime. He dazzled visitors by inviting them into his state-of-the-art laboratory, performing surgery on rats while the visitors watched, and discussing the significance of his findings in whatever language they spoke best.

Selye first encountered the problem that dominated his career as a second-year medical student at the University of Prague. His professor presented the medical students with five patients suffering from different diseases. The professor carefully questioned and examined each patient as the future physicians looked on. Though each patient suffered from a different disease, they shared several common symptoms, such as a coated tongue, aches and pains in the joints, intestinal disturbances, and appetite loss. Most patients had a fever; some had skin rashes and inflamed tonsils, spleens, and livers. Selye's professor ignored these shared symptoms, instead focusing on how certain symptoms were diagnosed; for example, little red-and-white "Koplik spots" on the inside of the cheeks near the molars indicated measles.

Selye, in contrast, was very excited about the symptoms that characterized "the syndrome of just being sick," as he originally called it. What caused this common suite of physiological responses? He wondered why nobody else seemed to pay any attention to this syndrome. Of course, there was no way a 19-year-old medical student could convince anyone to pay attention to his finding, which most people regarded as trivial and unworthy of serious consideration.

SEARCHING FOR NEW OVARIAN HORMONES

Selye's insight became more important a decade later in 1936, as he began his career as a postdoctoral biomedical researcher at McGill University in Montreal. His professor, J. B. Collip, was searching for new ovarian hormones, so Selye's first task was to retrieve a bucket of fresh cow ovaries from the slaughterhouse. Collip ground the ovaries and prepared extracts with different solvents. Selye then tested these extracts on some female rats.

A few days after injecting his first rats with one of the extract solutions, Selye killed the rats and performed autopsies, hoping to find anatomical changes. If the treated rats showed changes in response to the extract treatment, he would have evidence for a new hormone. Much to his joy, he discovered the following triad of anatomical changes:

1. considerable enlargement of the adrenal cortex (outer layer of the adrenal gland, located just above the kidneys),
2. intense shrinking of the lymphatic structures, including the thymus, spleen, and lymph nodes, and a major reduction in the number of eosinophils (a type of white blood cell associated with immune response),
3. deep ulcers in the lining of the stomach and duodenum (Figure 10.2).

No ovarian hormone had ever been shown to induce these changes, and Selye was enthusiastic about his good fortune. Next, he tested extracts of the placenta which had already been shown to produce other sex hormones. He discovered the same anatomical changes. When he tried extract of the pituitary gland (located at the base of the brain), he was astounded to find the same effect. Why should three different glands produce the same hormone?

One hypothesis was that the rats were reacting not to a specific hormone in the extract, but rather to the pain and stress of being handled, jabbed with needles, and kept under less than ideal conditions by an inexperienced researcher. As an endocri-

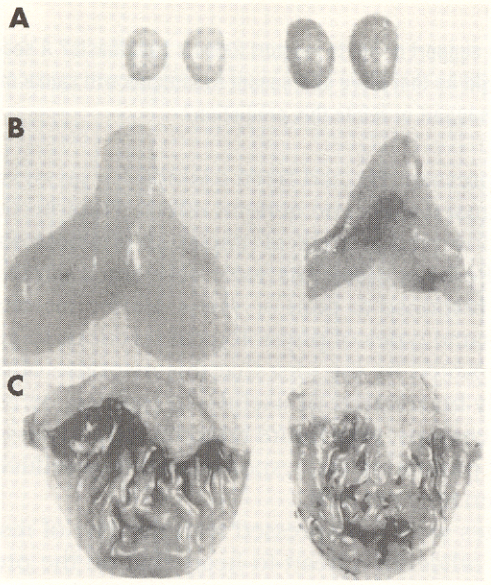

FIGURE 10.2 Common anatomical response to stress during the alarm reaction. The pictures on the left are from a normal rat, while those on the right are from a rat that was immobilized on a board for 24 hours prior to being sacrificed. Notice the (A) enlargement of the adrenals, (B) shrinking (involution) of the thymus, and (C) pitting and ulceration of the gastric mucosa. *Source:* from Hans Selye, *The Story of the Adaptation Syndrome.*

nologist embarked on the great search for a new ovarian hormone, Selye was not enthusiastic about this hypothesis. Yet it needed to be investigated.

How could he test this hypothesis? If his rats were showing a response to pain and stress, then any unpleasant stimulus should produce the same effects. He subjected six rats in each experimental group to a different potentially stressful stimulus, leaving one group of six rats as a control. The accompanying table shows the response of thymus and adrenal glands to stressful stimuli.

Treatment	Mean Thymus Weight (mg)	Mean Adrenal Weight (mg)
Control (untreated)	281	50
Starved for 96 hours	80	56
Exposed to 5°–7° C for 48 hours	102	65
Legs tied for 48 hours	82	68
Extensive skin lesions	104	45
Fracturing both tibias and femurs	145	50
Removing intestines from body for 1 minute	100	66
Atropine (2 cc of 1% solution, 4 times over 2 days)	55	64
Morphine (2 cc of 1% solution, 4 times over 2 days)	78	49
Epinephrine (0.1 cc of 0.1% sol., 4 times over 2 days)	84	44
Formaldehyde (0.5 cc of 4% sol., 4 times over 2 days)	64	60

PROBLEM

In what ways do these results support or fail to support Selye's hypothesis? A second prediction of Selye's hypothesis might be that more unpleasant treatments will cause more pronounced effects. Do the data support or refute this prediction?

Selye was seriously depressed. He had been looking for an ovarian hormone, but almost any treatment caused the same general effect. Then he flashed back to the human patients he had observed in medical school, all of whom shared the "syndrome of just being sick." Perhaps these rats were showing a similar syndrome—some sort of physiological response to pain or stress. Maybe his rats and the sick humans were showing the same types of physiological reactions to general trauma.

Selye was particularly excited by the idea that this response of the body to all types of stress might actually be adaptive or useful—in essence, be Nature's way of fighting disease and injury. Perhaps, with future research, physicians could help this defensive process along by promoting the response, and thus reduce the suffering that people go through when they are sick.

Most of Selye's associates were unimpressed with this line of research. In fact, Collip called Selye into his office for a heart-to-heart chat on the problems of this research plan. Collip explained that Selye had the potential to be a successful endocrinologist, so why was he wasting his time looking for a general effect that could be caused by any substance or treatment? As Collip stated emphatically, "But, Selye, try to realize what you are doing before it is too late. You have now decided to spend your entire life studying the pharmacology of dirt!"

Despite a lack of enthusiasm by his colleagues, Selye persisted and, in fact, devoted the rest of his life to studying this process, which he called the **stress response**. One of the most difficult, challenging, and stimulating problems faced by a scientist is to decide what to do with a new idea. Is the idea really worth pursuing? If so, how should it be pursued? What are the important questions? What avenues of investigation will be fruitful, and what avenues will lead to dead ends?

Selye knew that some of the affected structures had already been shown to be important sources of hormones. He reasoned that if these anatomical changes affect hormone release, then there should be behavioral or physiological responses to stress. He also knew from his autopsy studies that the anatomical changes often went away, even if the source of stress continued. In fact, the animals subjected to continued stress appeared to be more resistant to additional stress. He wanted to know whether his reasoning and impressions were correct. Specifically, how does resistance to stress change over time? Also, does exposure to a stressor make the individual more resistant to other sources of stress?

In an experiment designed to answer these two questions, Selye used moderate cold (2° C) as the first stressor, and extreme cold (-4° C) as a second source of stress. He autopsied 10 rats from each group; all cold-treated rats showed the triad of anatomical changes, while none of the control group showed any anatomical changes. Selye then transferred 20 of the remaining 90 cold-treated rats to an even colder chamber (-4° C) along with 20 of the remaining controls. The accompanying table shows the experimental design.

Time	*N*	Experimental Group	*N*	Control Group	Experimental Comparison
0	100	Keep at 2° C for 48 hours	100	Keep at 20° C for 48 hours	
48 hours	10 20 70	Autopsy Move to -4° C Stay at 2° C for 5 weeks	10 20 70	Autopsy Move to -4° C Stay at 20° C for 5 weeks	Compare anatomy Compare survival
5 weeks	20	Move to -4° C	20	Move to -4° C	Compare survival
Until Death	50	Stay at 2° C	50	Stay at 20° C	Compare survival

N = number of rats receiving each treatment

Selye found that the control rats survived much better than the cold-treated rats following the transfer to -4° C.

PROBLEM

Propose a hypothesis to explain why the control rats survived better when moved into the subzero temperatures at 48 hours.

Selye wanted to know whether the same pattern would hold after a longer continuous exposure to the 2° cold treatment. His early studies had shown that the triad of anatomical changes was in some cases reversed by five weeks of constant exposure to stress. Would rats exposed to constant cold for a long period of time be more resistant than rats exposed to cold for 48 hours? After exposing his experimental rats to 2° C for five weeks, Selye transferred 20 more of these cold-treated rats and 20 untreated controls to -4° C. In contrast to his findings at 48 hours, Selye found that the cold-treated rats had a much higher survival rate than the controls following the transfer to -4° C. What could account for these findings?

Was there some long-term cost to the rats from being continuously exposed to the stressful stimulus? Selye allowed his 50 surviving cold-treated rats to live out their remaining lives at 2° C, while his 50 remaining untreated controls continued a more normal 20° C existence. He found that the cold-treated rats had much shorter life spans than the untreated controls.

THE GENERAL ADAPTATION SYNDROME

On the basis of this and other experiments conducted during the mid- and late 1930s, Selye constructed a three-stage model of physiological response to pain or stress that he called the **General Adaptation Syndrome (GAS)**. The first stage is the *alarm reaction*, in which the body makes its initial response to the stressful stimulus. Anatomical changes during this period include the triad of responses Selye discovered in his first experiments (Figure 10.2). Other researchers stimulated by his findings replicated his experiment and were able to show a more consistent increase in the adrenal gland than Selye had shown. Selye also found major physiological changes in the early part of the alarm reaction (which he called "the shock phase"),

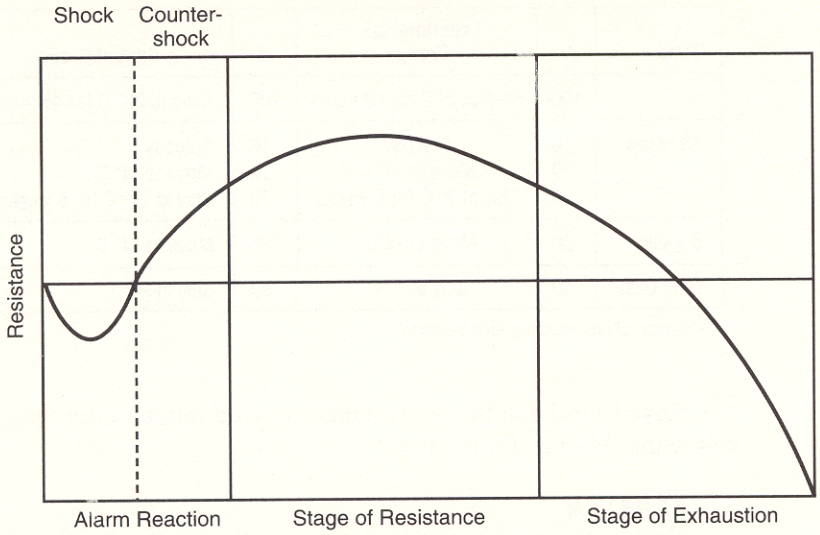

FIGURE 10.3 Schematic representation of the changes in resistance during the three stages of the GAS. Resistance to the stressor decreases during the shock phase of the alarm reaction and increases during the countershock phase, reaching its maximum during the stage of resistance. In the stage of exhaustion, it falls below normal and, finally, the animal dies.

including reduction in blood pressure, hypothermia, decrease in muscle tone, and depression of the nervous system. Most of these anatomical and physiological changes are reversed during the latter part of the alarm reaction ("countershock phase"), after the body begins to respond to the hormones that are released into the bloodstream (see Figure 10.3 for a graphical representation of the GAS).

If the source of stress persists, the body enters the second stage of the GAS, which is the *stage of resistance* or *stage of adaptation.* During this stage, the body shows increased resistance to the particular stressor to which it is being exposed. The triad of anatomical responses disappears or is greatly reduced; thus, the animal has adapted to the stressful stimulus.

With continued exposure to the same stressor, the animal enters the final stage of the GAS, which is the *stage of exhaustion.* During this stage, the animal experiences a reoccurrence of the symptoms of the alarm reaction and appears to lose the adaptation it has developed in the second stage. If the stage of exhaustion continues for too long, the animal dies.

PROBLEM

Use Selye's GAS model to interpret the findings of his experiments with cold-stressed rats. In which stages of the GAS were the cold-stressed rats during each part of Selye's experiment?

The GAS describes what happens during stress without really explaining why these changes occur. Selye proposed that hormonal changes were responsible for the results of his experiments with stress. Based on the observed anatomical changes, he

hypothesized that the adrenal and thymus glands released hormones that controlled the stress response.

Why did animals lose their resistance during the final stages of the GAS? Selye proposed that, at birth, individuals have a finite quantity of "adaptation energy," which is gradually consumed by exposure to a stressor. When all the adaptation energy is used up, the animal dies. Selye proposed that adaptation energy can be partially restored by rest and healing but that an individual's life span is shortened by periods of stress.

PROBLEM

How could Selye test his concept of adaptation energy? What challenges are associated with designing such a test?

How Does the Stress Reaction Work?

Selye provided a description of several different changes that occur in the body in response to different types of stressors. His challenge was to generate an accurate picture of what actually happens within the body of a stressed animal.

When Selye was doing his work, the adrenal medulla had already been shown to secrete the hormone epinephrine (also known as adrenaline), which raised blood pressure in response to stressors (see Chapter 9). He knew that the medulla had some role in the very early part of the shock phase. But the increase in the size of the adrenal gland during the alarm stage was due to an increase in the size of the cortex of the adrenal gland—not the medulla. Selye wanted to know if the increase in the adrenal cortex caused the decrease in the thymus.

This idea was stimulated, in part, by work in several other laboratories, where researchers were feverishly attempting to characterize the hormone produced by the adrenal cortex. This unidentified hormone—initially named "cortin"—was produced by grinding up a cow's adrenal cortex and putting the grounds through a series of solvents. This extract was then injected into research animals. As research on this substance continued, many techniques of purification were developed, but the active ingredient itself was still unknown. Using the available technology, Selye conducted a series of experiments to determine more precisely the adrenal gland's role in the stress response.

Selye removed the entire adrenal glands of a group of rats and left the adrenal glands intact in several groups. He subjected the rats to stressors of various types; in addition, all rats except the untreated controls were starved during the course of the experiment. Selye discovered that rats without adrenal glands showed only a slight reduction in thymus size. Two groups of rats were given high doses of cortin or epinephrine (adrenaline in Figure 10.4). Even these rats showed only a slight reduction in thymus size.

PROBLEM

How do the findings in Figure 10.4 support or refute Selye's claim that hormones produced by the adrenal glands shrink the thymus gland during the stress response? Design your own experiment to investigate this question.

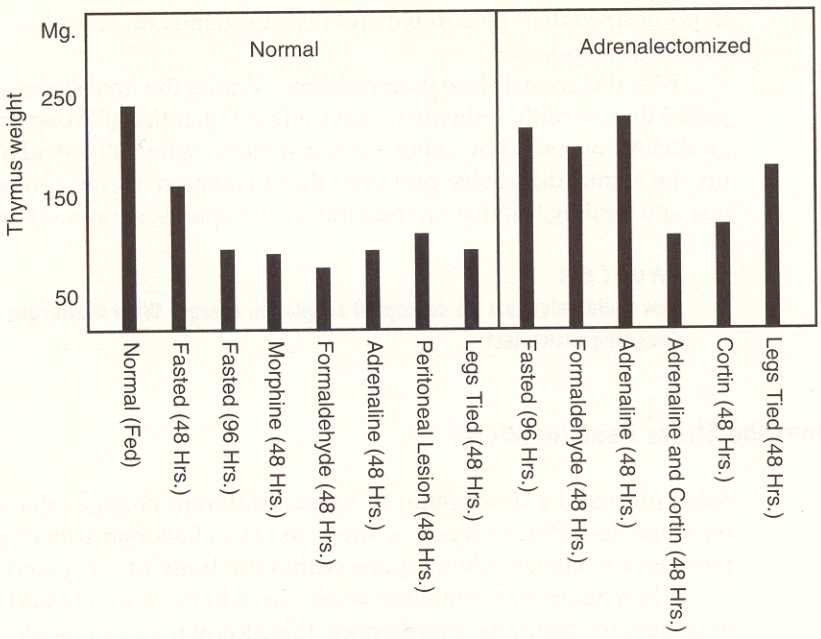

FIGURE 10.4 Thymus weight in rats in response to stress. Rats from the groups on the right had their adrenal glands removed before being subjected to food deprivation. Two of these groups of rats were injected with adrenal gland hormonal extracts. *Source:* Hans Selye, "The General Adaptation Syndrome and the Diseases of Adaptation," *Journal of Clinical Endocrinology and Metabolism* 6: 117–230.

Diseases of Adaptation

As Selye describes in his writings, part of the motivation for his career choice was a humanistic interest in eliminating disease. He hoped that understanding the stress response would allow him to help eliminate or reduce the trauma of certain diseases.

Many of the symptoms of the stress reaction were very similar to symptoms of diseases that were commonly afflicting people during the first part of the twentieth century. For example, animals during the stage of exhaustion sometimes developed serious kidney diseases, often accompanied by inflamed arteries, proteins excreted in the urine, high blood pressure, and the formation of nodules on the heart tissue. Selye hypothesized that these diseases were actually diseases of adaptation caused by excessive production of cortical hormone in response to stress. While high cortical production allowed the animal to deal with short-term stress, over the long haul, continued cortical production exhausted the animal's adaptation energy, leading to serious disease and possibly death.

Selye reasoned that if he was correct he should be able to induce symptoms of diseases of adaptation by injecting rats with high levels of cortical extract. Biochemists had recently developed techniques for producing significant amounts of deoxycorticosterone acetate (DCA), a hormone that affects salt and water metabo-

lism. Selye administered high doses of DCA to experimental rats, fed them high-salt diets, and removed one of their kidneys. In response to this treatment, rats developed some of the symptoms of naturally occurring kidney diseases. Selye concluded that he had shown that one of the principal causes of these diseases was excessive secretion of DCA, or substances similar to DCA, in response to stress. Was this conclusion justified?

THE MIXED RECEPTION OF SELYE'S RESEARCH

Most scientists at the time were convinced by Selye's research that the general adaptation syndrome was an accurate description of how animals respond to stress and had important implications for understanding human health questions. Yet many of these same scientists were skeptical about Selye's application of his findings to human health concerns.

Three factors weakened Selye's hypotheses and ultimately reduced the stature of his theories. First, scientists objected to Selye's description of the mechanism underlying the syndrome. There was virtually no evidence that there was such an entity as adaptation energy, and Selye was never able to demonstrate that people or rats ever exhausted anything as part of the stress reaction.

Second, endocrinologists had difficulty replicating Selye's results with DCA and kidney disease. Many scientists objected to the high doses and artificial conditions required before the rat developed its symptoms. Finally, research by physiologists demonstrated that DCA was a relatively unimportant hormone in the body; thus, results obtained with DCA were not physiologically relevant. This last point was simply bad luck on Selye's part, as no endocrinologist at that time knew that DCA was not physiologically active.

But the most critical factor refuting the concept of diseases of adaptation was the discovery that cortical hormones had dramatic anti-inflammatory effects, which earned Edward C. Kendall and Philip S. Hench the Nobel Prize in 1950. In his autobiography, Kendall describes the first rheumatoid arthritis patient to be given compound E (later named cortisone) as being unable to walk as a result of the debilitating pain she was suffering. Seven days later, this same woman shopped for three hours downtown and stated, "I have never felt better in my life." There was now hope for the three million people who suffered from this disease in the United States alone. While the world rejoiced, Selye's hypothesized diseases of adaptation were dealt a fatal blow.

Why was Selye held in such high regard in the 1930s and 1940s? Several factors were in his favor. During his early career, he did some excellent science. He saw a pattern of physiological response that many other scientists had seen, but was unique in identifying its importance for understanding how the body works.

Additionally, his general adaptation syndrome and the related hypothesis of diseases of adaptation very neatly tied together a hodgepodge of otherwise perplexing observations and experimental results. Selye's interpretations of the data were reasonable and insightful, based on the information available to him at that time.

☐ EPILOGUE

Selye's contribution to the field of endocrinology survives him and his ideas. Though the term *general adaptation syndrome* is rarely used by modern endocrinologists, studies of stress physiology and the activity of cortical hormones continue today at a much more intense pace than during Selye's time. Currently, about twenty hormones have been shown to be involved in the stress response. Small wonder, then, that administration of one hormone gave ambiguous results in experiments conducted by Selye and others who attempted to replicate his experiments. Researchers have also shown that chronic activation of the stress response is damaging to health and that people with hard-driving (Type A) personalities have a higher risk of hypertension and heart disease.

In addition to stimulating physiological research into the stress response, Selye extended his ideas outside of the traditional scope of biology. During his last decade, Selye promoted the social implications of the stress response to psychologists, sociologists, and administrators of many different types of organizations, who make stress reduction and management an important goal for economic and personal satisfaction.

QUESTIONS AND ACTIVITIES

1. What does this case show about the following aspects of doing biology?
   — tenacity in pursuing research objectives
   — the effect of background and perspective on the process of discovery
   — the importance of replicating experiments
   — consideration of alternative explanations of findings
   — the use of models in biology
2. Design an experiment that allows you to test whether the increased resistance to a stressor characteristic of the stage of resistance confers resistance to other stressors as well. Limit yourself to 100 rats. Be as specific as possible. What type of stressor would you use? What information would you need to know to determine when to subject your rats to the stressors? What would you measure?
3. Did you consider the ethics of research on animals in the previous question? What constitutes ethical treatment of animals for experiments?
4. A tremendous number of rats were being traumatized and then killed by Selye's manipulations. Can you think of any alternative designs that would test Selye's hypothesis that the triad of anatomical changes is a general response to pain or stress? More generally, in what ways (if any) should scientists consider the discomfort they cause their subjects when choosing research questions and designing experiments?
5. Propose a hypothesis for why cold-stressed rats have much shorter life spans than rats raised at normal temperatures. What types of observations or experiments could you do to test this hypothesis?

6. To test his idea of diseases of adaptation, Selye injected rats with high levels of cortical extract. Some of his rats showed some symptoms of kidney disease. Assume instead that all of his rats developed serious disease symptoms. What could you reasonably conclude from this finding? What experiment would you do next to follow up on this result?

SUGGESTED READING

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