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In Retrospect

Eighty years of stress

The discovery in 1936 that rats respond to various damaging stimuli with a general response that involves alarm, resistance and exhaustion launched the discipline of stress research.

GEORGE FINK

Modern research into biological stress — the physiological response of an organism to stressful stimuli — spans broad disciplines, from genetics to endocrinology to brain imaging. Much of this diverse field has a shared origin in a landmark paper published 80 years ago in *Nature*[1]. In this brief note, the biologist Hans Selye described a common physiological response in rats subjected to a diverse range of harmful factors; he named this the stress response[2]. Selye's observation set the scene for decades of future discoveries.

The history of stress research begins in the mid-nineteenth century with the physiologist Claude Bernard[3], who proposed that the cells of the body are bathed in a fixed internal environment that is maintained in the face of changing external conditions by compensatory physiological changes. In the early twentieth century, this concept was termed homeostasis by another physiologist, Walter Cannon[4]. Cannon described how animals react to stimuli that threaten homeostasis with a physiological response that he dubbed 'fight or flight'.

In his 1936 paper, Selye reported that when rats were subjected to nonspecific damaging agents such as exposure to cold, surgical injury or intoxication with diverse drugs, they showed a typical response that was not dependent on the nature of the agent. He described three phases to this general adaptation syndrome (GAS): alarm, resistance and exhaustion. Alarm corresponds to the fight-or-flight response described by Cannon; resistance to a period in which the body adapts to repeated exposure to the stress; and exhaustion to a relapse of symptoms that occurs if the stress is exerted for too long. The main features of the syndrome were suppression of the immune system, ulceration of the lining of the stomach and small intestine, and activation of the two main neuronally activated stress-response systems — the hypothalamic–pituitary–adrenocortical (HPA) axis and the sympathomedullary system (Fig. 1).

In the HPA axis, activation of nerves in the brain's hypothalamus triggers release of the hormone corticotropin-releasing factor (CRF), which in turn causes secretion of the hormone adrenocorticotropin (ACTH) from the pituitary gland at the base of the brain into the blood. ACTH stimulates secretion of hormones, including cortisol, from the cortex of the adrenal gland. Hypothalamic signalling also triggers the sympathomedullary system, which increases heart rate, shunts blood from the skin and gut towards the skeletal muscles, and releases adrenaline from the medulla region of the adrenal gland. Adrenaline and cortisol act synergistically to increase levels of glucose in the blood[5], providing the energy required for fight or flight.

Selye defined stress as "the nonspecific response of the body to any demand"[2,6,7]. He believed that stress was different from emotional arousal or nervous tension[6] because, as he wrote, the same general response was known to occur under or in response to anaesthesia in humans and animals, and also to occur in plants and bacteria, which have no nervous system (the generality of this response is reviewed in refs 8 and 9). Thus, he concluded, stress has a key protective role in all organisms. Moreover, he correctly proposed that the stress response is the same whether a stimulus is pleasant or unpleasant — the key factor is whether the intensity of the stimulus necessitates adaptation[7].

The biologist's views and definition of stress were widely accepted, although not without resistance[6,10]. In fact, recognition of the fact that stress is not necessarily due to nervous arousal encouraged many scientists and clinicians to use the more precise terms neurogenic stress and psychogenic stress[6].

Selye recognized that maintaining an internal physiological balance through homeostasis (stability through constancy) could not by itself ensure the stability of body systems under stress, and he coined the term heterostasis to describe the process by which a new steady state could be achieved through adaptive mechanisms[7]. The idea of heterostasis can be considered a forerunner to the discovery, in the late 1980s, that neural regulation of feedback in various body systems can alter physiological responses to enable animals to meet a stressful challenge[11–13]: a phenomenon known as allostasis (stability through change).

From allostasis has sprung the idea that the amount of stress to which an individual

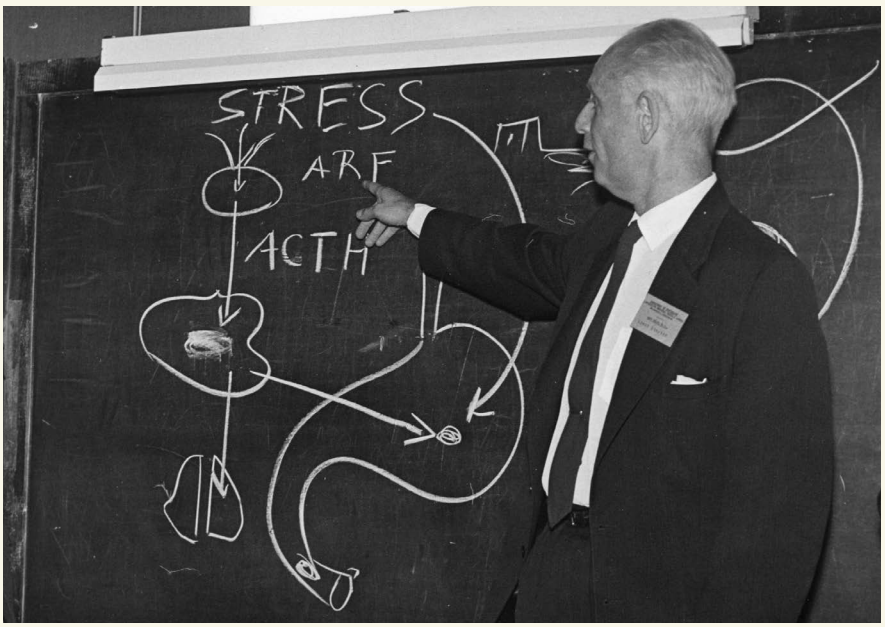

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Figure 1 | Hans Selye outlines the general adaptation syndrome. In 1936, the biologist Hans Selye observed a stress response in rats subjected to a range of potentially harmful stimuli[1]. The syndrome involves three phases: alarm, resistance and exhaustion (ARE). Release of the hormone adrenocorticotropin (ACTH) in response to stress stimulates secretion of multiple hormones from the adrenal gland, affecting many organs and systems, including the thymus glands and stomach (pictured).

is subjected over time can be quantified by measuring adverse effects on the cardiovascular and other organ systems[13]. Further research is required to determine how best to quantify this allostatic load to provide a robust index of stress. It also remains to be seen whether and how such an index could be applied in the clinic.

A growing understanding of stress led to an ability to modulate stress-response pathways to treat disease. In 1950, the Nobel Prize in Physiology or Medicine was awarded for the first use of synthetic adrenocortical hormones, such as synthetic cortisol, as powerful anti-inflammatory agents for treating conditions such as rheumatoid arthritis.

In 1981, the amino-acid sequence of CRF was characterized[14]. Selye died in 1982, and so did not witness the quantum leap in our understanding of stress that followed. The structure of CRF, the characterization of its receptors, and the development of investigative tools such as molecular genetics and brain imaging have allowed us to map the structure and function of brain pathways involved in the stress response. These advances have facilitated our understanding of the neural mechanisms involved in many mental disorders, including anxiety, depression and post-traumatic stress, and provided targets for therapies to treat these disorders.

However, many uncertainties remain[15]. These include the extent to which genetic mechanisms determine susceptibility or resilience to stress, and whether some people are genetically more susceptible to post-traumatic stress than others. It is unclear whether genetic predisposition to stress susceptibility can be affected by the environment, either in the womb or after birth, and whether this type of susceptibility can be transmitted between generations. Another question facing researchers is whether stress-induced changes in brain chemistry, which occur in major depression and anxiety, might damage the human brain, reversibly or irreversibly.

The holy grail for many stress neurobiologists is to find a way to selectively extinguish adverse post-traumatic memories. The chances of such a discovery in the near future are perhaps remote, given the complexity of the human brain and the accompanying ethical issues. Nonetheless, it would doubtless benefit many people who have post-traumatic stress and other mental disorders.

We now know that, although GAS as described by Selye sometimes manifests in people who experience extreme stress such as septic shock or multiple traumatic injuries, some components of GAS, such as stomach ulcers, are not useful quantitative clinical indicators of stress. Modern markers of stress include behavioural observations and hormonal measurements of sympathomedullary and HPA activation. As such, the scientific and clinical currency of GAS has diminished over time. Nonetheless, it retains its importance in launching the stress field. Eighty years later, the foundations laid by Selye are still being built on. ■

George Fink *is at the Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria 3010, Australia.*
e-mail: george.fink@florey.edu.au

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