Chapter One

Evaluating the Role of Hans Selye in the Modern History of Stress

Mark Jackson

> This is the philosophical point of view which alters our concept of disease. . . . Medical men who recognize the revolutionary and shattering nature of these developments realize that a great adjustment in our thinking has to be made. Here is the pool of Bethesda.
>
> J. S. L. Browne, "New Pool of Bethesda"

> Some years ago, Hans Selye postulated a general adaptation syndrome due to stress, but this concept has been of doubtful value in advancing the understanding of maladies.
>
> John W. Todd, "Plain Words in Medicine"

According to many stress researchers, as well as historians, modern biological formulations of stress can be traced back to a brief and rather speculative article written by the Austrian-born Hungarian scientist Hans Selye (1907–82) in 1936. The article set out what appeared to be a characteristic triphasic pattern of nonspecific physiological responses to injury: the "general adaptation syndrome" comprised an initial alarm phase that was followed by a stage of resistance or adaptation, leading eventually to a stage of exhaustion and death.[1] Within traditional narratives of stress history, which have often been written by researchers themselves and which portray the origins and development of scientific understandings of stress as relatively unproblematic and progressive, it was the general adaptation syndrome, or what Selye sometimes referred to rather ostentatiously as "Selye's syndrome," that provided a conceptual framework for Selye and his colleagues to develop a complex neurohormonal model of stress that implicated pituitary and adrenal function in the etiology of many chronic diseases, such as hypertension, peptic ulceration, renal disease, arthritis, asthma, and cancer.[2]

In later reflections on the intellectual origins of the general adaptation syndrome, Selye claimed that his insights into biological stress were not only the serendipitous product of a series of laboratory experiments performed on rats in the Department of Biochemistry at McGill University in Montreal, during which he had been attempting to isolate a new ovarian hormone. They were also the result of his clinical experiences as a medical student in Prague during the 1920s, when he had been struck by the similar sickly appearance of patients suffering from diverse chronic conditions such as tuberculosis, cancer, and burns: "All five patients, whatever their disease . . . had something in common," he wrote in his autobiography many years later. "*They all looked and felt sick.*"[3] It was primarily these personal encounters with patients in the clinic and observations in the laboratory, Selye insisted, that had led him to suggest that many clinical features of disease were the result of a failure in the nonspecific adaptive mechanisms of the body.

Selye's emphasis on his own pioneering contributions to the field has been reiterated in other historical accounts, which have juxtaposed analysis of his scientific status with more controversial anecdotal evidence of his commitment and character to highlight his role in shaping and popularizing modern formulations of stress. In 1975 John W. Mason, a neuroendocrinologist at the Walter Reed Army Institute of Research in Washington, suggested that the importance of Selye's work had led many researchers to assume (wrongly, according to Mason) that "usage of the term 'stress,' in a biological sense, begins historically with Selye's publications."[4] Although Mason pointed to earlier usage of the term and parallel formulations of the links between emotional stress and disease, he nevertheless acknowledged that Selye's 1936 paper on adaptation and disease had become part of the canon of stress literature, constituting a primary point of reference for scholars throughout the world regardless of their disciplinary orientation or focus. Historians have often perpetuated the conviction that Selye's article constituted a turning point in the history of stress and have occasionally acclaimed Selye as the creator, or father, of stress.[5]

These assessments of Selye's impact on the development of stress research are not entirely misplaced. During the 1930s, 1940s, and 1950s, Selye and his colleagues authored an expansive number of articles and monographs that clearly shaped and energized biological, and indeed psychological, studies of stress. Not only did Selye's reputation attract scholars from around the world to his research institutes, but Selye himself also became a much sought-after speaker on stress and health in many countries. In recognition of his contributions to stress research, Selye was nominated for the Nobel Prize in Physiology or Medicine seventeen times between 1949 and 1953, particularly for his "work on endocrinology and the adaptation syndrome," for his contributions to the "isolation of steroid hormones," and for his formulation of "stress reactions."[6] Although influential, Selye's

theories of adaptation and stress were not unequivocally accepted by his contemporaries or indeed by his students: on the contrary, his experimental methods, his conceptual framework, and his entrepreneurial style were all strongly challenged, and many of his findings were eventually discarded. Nevertheless, as many of the chapters in this book indicate, during the middle decades of the twentieth century, Selye's notion of biological stress and its impact on health was adopted and adapted by researchers in a variety of adjacent fields, including military medicine, veterinary medicine, clinical allergy, sociobiology, population studies, cybernetics, and psychiatry.[7]

In spite of Selye's apparent prominence in the history of stress research, there have been few critical evaluations of the intellectual and cultural determinants of Selye's theories, few challenges to Selye's self-composed narrative of creation and progress, and few attempts to explore the heterogeneity of scientific responses to his ideas. Biographical accounts of his life and historical overviews of his contributions to modern understandings of stress have been based predominantly on his popular, often superficial and self-promoting, publications rather than on his more detailed scientific endeavors or archival sources.[8] Previous studies have tended toward polarized interpretations: at one extreme, many of those who worked closely with him in Montreal have regarded Selye, rather uncritically, as the preeminent figure in the field, responsible almost single-handedly for constructing and promoting a link between adaptation, stress, and organic disease; at the other extreme, historians and social scientists, wary perhaps of the hagiographic tendencies of scientific biography, have been more openly skeptical, pointing to Selye's capacity for entrepreneurship and media manipulation and playing down his scientific credibility. Closer inspection of his extensive output on the physiology and biochemistry of stress and analysis of contemporary reactions to his ideas suggest a more complex, and more intriguing, story. By focusing in turn on his theories of adaptation, his studies of steroid hormones, and his growing preoccupations with the language and mastery of stress, this chapter argues that, although his work was rigorously contested, Selye provided an important methodological platform for scientists and clinicians interested in understanding the relationship between stressful modern lives and disease.

The General Adaptation Syndrome

Born in Austria in 1907, Hans Selye was brought up in Komárom, on the border between Czechoslovakia and Hungary. After completing his medical degree and a doctorate in organic chemistry at the German University of Prague, he received a Rockefeller Foundation fellowship to study at Johns Hopkins in Baltimore before he moved to the Department of Biochemistry

Figure 1.1. Hans Selye, 1956. Photograph by Chris Lund. National Film Board of Canada, Library and Archives Canada (PA-116671).

at McGill University in Montreal, under the sponsorship of James Bertram Collip (1892–1965), a biochemist who had discovered the parathyroid hormone and had been a member of the team responsible for isolating insulin in the 1920s. Selye's early work at McGill focused on the identification of ovarian hormones. It was in one of the papers emanating from this research in 1935, coauthored with Thomas McKeown (1912–88), who had been in Montreal between 1932 and 1934 as a National Research Council–funded doctoral student, that Selye first used the word "stress" to describe the adverse circumstances to which laboratory animals were subjected during experiments.[9] However, it was a brief article in *Nature* the following year that established a rudimentary framework for Selye's subsequent formulation of biological stress.

According to Selye, experiments on rats indicated that biological responses to "nocuous agents," such as cold, surgical injury, excessive exercise, or sublethal doses of drugs, demonstrated a stereotypical triphasic pattern irrespective of the nature of the injury: an initial alarm phase was followed by a stage of resistance that would lead eventually to exhaustion if exposure to the damaging agent persisted. Regarded by Selye as a form of defense similar to immunity, the general adaptation syndrome represented "a generalised effort of the organism to adapt itself to new conditions."[10] During the late 1930s and 1940s Selye explored the physiological stages of the general adaptation syndrome in more detail and clarified the central role of the adrenal glands in adaptive reactions.[11] In particular, he introduced the notion of "adaptation energy" to explain not only reduced tolerance to other forms of injury during the stage of resistance but also the eventual exhaustion and death suffered by laboratory animals after repeated exposure to environmental pressures. Using the weight of the thymus as an index of damage, Selye suggested that animals possessed only a finite capacity to adapt to injury: the cost of adaptation was the loss of "adaptation energy," a form of energy or resistance that was unrelated to calorific intake.[12] In subsequent formulations Selye referred to the loss of energy in terms of the "wear and tear" of life and drew a direct parallel between the stage of exhaustion on the one hand and processes of aging and dying on the other.[13]

Selye's most explicit exposition of his theory of adaptation and disease, at least prior to his wholesale adoption of the concept and language of stress, was an extended article published in 1946. More than one hundred pages long and containing nearly seven hundred references, this much-cited article established a model for Selye's regular overviews of the stress literature, which were published annually from 1950.[14] Selye situated his work primarily within studies of traumatic shock and toxicology, citing, for example, the work of the Harvard physiologist Walter Cannon (1871–1945), to whom the article was dedicated, and the American surgeon George W. Crile (1864–1943) on the physiological impact of surgical shock and the role of the nervous system in determining symptoms. Defining the general adaptation syndrome as "the sum of all non-specific, systemic reactions of the body which ensue upon long continued exposure to stress," Selye reviewed the biochemistry and pathological anatomy of adaptive responses, factors affecting the course of the general adaptation syndrome, and theoretical interpretations of the syndrome, including the pivotal role of hormones. He also set out the clinical implications of the general adaptation syndrome: "many of the most common maladies of man," he claimed, "are 'diseases of adaptation,' that is to say, the by-products of abnormal adaptive reactions to stress."[15]

Although Selye subsequently explained the genesis and parameters of the general adaptation syndrome primarily in terms of his personal endeavors, often relying largely on his own experimental results to substantiate

his arguments and claiming a relatively smooth process of translation from laboratory findings to clinical implications, his scientific publications and archival records suggest a more complex heritage. In particular, his work echoed, and sometimes directly drew on, preceding and adjacent studies of physiological adaptation, contemporary accounts of fatigue and anxiety among modern populations, and psychosomatic understandings of disease. In the first place the overarching framework of Selye's syndrome resonated with wider contemporary interest in adaptation. During the 1920s and 1930s it was not unusual for clinicians to regard an apparent increase in chronic diseases in Western societies in terms of faulty adaptation or adjustment to the environment. In 1923, for example, the British physician Francis G. Crookshank (1873–1933) highlighted the pivotal role of adaptation to external circumstances in shaping health and disease: while health comprised successful adaptation to the environment, disease constituted "a dissociation of functional unity, or, maladjustment due to failure or incompleteness of adaptive response."[16]

For Crookshank and others, the need for effective adaptation was particularly prominent among modern populations: "The fact is that, at the present time, social change—industrial, economic, and the like—is everywhere modifying the conditions of life more rapidly than we care to admit;—far more rapidly for the exercise of the *natural* powers of adaptation of the human race."[17] Clinical preoccupations with the impact on health of adapting to physical and mental trauma were evident elsewhere during the late nineteenth and early twentieth centuries: in accounts of railway spine; in George Beard's explanation for the increased prevalence of nervous disorders, such as neurasthenia, among modern, sensitive American populations; and in Adolf Meyer's (1866–1950) psychobiology, according to which abnormal behavior was understood in terms of a failure of adaptive responses. As Rhodri Hayward has argued, in a world threatened by social, political, and economic instability, the notion of adaptation became increasingly central to Anglo-American psychiatric, psychological, and neurological theory and practice during this period.[18]

Concerns about the impact of social and technological change on human health and on the limits of adaptability were clearly shaped not only by developments in physiology, which allowed scientists to measure more directly the impact of everyday life on the function of cells and bodies, but also by fears about increasing levels of mental stress, fatigue, and traumatic neurosis among industrial workers and soldiers.[19] Preoccupations with nervous energy, stress, and fatigue and attempts to address them were expressed in a variety of locations. In the late nineteenth century, for example, both mesmerism and yoga were advocated on the basis that they could restore or more effectively channel depleted energy.[20] The sale and consumption of nerve tonics, such as Phosferine, Phyllosan, and Sanatogen, rested on claims

that such proprietary preparations would help to combat what appeared to be an epidemic of anxiety, fatigue, nervous stress, and strain induced by the "modern conditions of high-pressure living." In a similar fashion, more orthodox physiological studies of shock, exhaustion, and the origins and nature of the emotions by George W. Crile, whose work was well known to Selye, highlighted the manner in which "noci-influences" operated to cause disease through the discharge of nervous energy.[21]

Similarities between Selye's and Crile's accounts of adaptation and disease are striking. At a general level Crile claimed that physiological systems were being driven at "an overwhelming rate of speed" by the "stress of our present-day life." Both acute and prolonged overstimulation by physical or emotional trauma placed the body "under stress," leading to the release of adrenaline and disturbing the previously "evenly balanced work" of the organs, especially those responsible for bearing "the stress of life," namely the brain, adrenal glands, and liver. Echoing previous discussions of neurasthenia and insanity, Crile implicated a variety of stresses in the etiology of chronic disease, including emotional strain, infection, physical labor, pregnancy, and "the stress of business or professional life." Cases of diabetes, like neurasthenia, were supposedly more prevalent among Jews, who were regarded as "especially emotional in character," and among businessmen concerned about the price of stocks. Although Crile acknowledged that adaptability, or the precise levels of "adaptive energy," varied between individuals (as well as between species) and although he accepted that different organs sometimes failed under stress, giving rise to different clinical manifestations, he emphasized what became a key feature of Selye's subsequent approach to stress and disease, namely the nonspecific nature of the pathological manifestations of responses to shock and trauma: "The essential pathology of shock," Crile insisted, "is identical whatever the cause."[22]

Energy, fatigue, and stress were also familiar motifs in accounts of the impact of work and war on the health and efficiency of what Anson Rabinbach has referred to as the "human motor." In his presidential address to the American Philosophical Society in 1906, the Harvard psychologist William James (1842–1910) encouraged colleagues to explore "the amount of energy" required and available for mental and moral activities and praised the ability of yoga to stabilize the nervous system and restore or unleash "unused reservoirs of power." Shortly after World War I, many of the witnesses to the British War Office inquiry into shell shock attributed the condition to prolonged and severe mental stress and fatigue: according to W. H. R. Rivers (1864–1922), for example, shell shock was largely the product of "stress, using stress as a wide term, including sleeplessness, anxiety, fatigue, responsibility."[23] Mental and physical disturbances associated with warfare in the air were similarly explained in terms of the strain, fatigue, and anxiety generated by prolonged flying and the conscious suppression of

fear.[24] During the 1930s and 1940s much of the work at the Harvard Fatigue Laboratory, established in 1927 under the directorship of Lawrence J. Henderson (1878–1942), also concentrated on studying adaptive responses to physical stress and fatigue.[25]

It is not clear whether Selye was influenced directly by these studies of the fatigue and stress caused by modern life. In his discussions of adaptation energy and exhaustion he tended to cite the result of his own experiments rather than refer to any broader literature to support his arguments. It is clear, however, that Selye's formulation of the general adaptation syndrome did draw heavily on closely related interwar studies of physiological stability and self-regulation, on which scientific and clinical discussions of fatigue were partly based. Although stability constituted a crucial concept in contemporary debates about psychological health, scientific and medical interest in adaptive stability was most evident in the laboratory investigations of Walter Cannon.[26] During the 1920s Cannon published a number of key papers on the regulatory mechanisms by which organisms controlled a variety of internal conditions, such as blood glucose and salt concentrations, temperature, and acid-base balance. Cannon emphasized the manner in which these physiological processes were regulated by carefully coordinated cooperation between the autonomic nervous system and the endocrine glands, introducing the term "homeostasis" to describe the adaptive mechanisms that preserved functional stability in the face of environmental change.[27] In addition, he highlighted the clinical significance of these findings: deficient or uncontrolled hormonal secretion, particularly from the pituitary, thyroid, and adrenal glands, stimulated by "great emotional stress," he argued, could "play havoc with our internal adjustments" and generate disease.[28]

Cannon's account of self-regulatory adaptive processes clearly provided an important context for Selye's formulation of the general adaptation syndrome: Selye's 1946 article was dedicated to Cannon; Selye discussed Cannon's physiology at length in most of his books on adaptation and stress; and many of Cannon's publications appeared in Selye's extensive bibliographies. In 1975 Selye also contributed two chapters to a posthumous Festschrift for Cannon, in which he referred to Cannon as "one of the greatest physiologists not only of this century, but of all time" and suggested that, along with Claude Bernard, Cannon had exerted the greatest influence on his formulation of the general adaptation syndrome.[29] It may well be that Selye's subsequent adoption of the term "stress" also owes much to the work of Cannon, who had incorporated notions of stress in his accounts of homeostasis and emphasized the role of emotions in precipitating stresses and strains on the nervous system.[30] In addition, Cannon's elaboration of what he termed "social homeostasis" provided the blueprint for Selye's subsequent construction of a "natural philosophy of life," designed to maintain or restore individual happiness and social stability.[31]

Adjacent developments in clinical medicine may also have shaped Selye's preoccupation with adaptation and disease. Proponents of psychosomatic medicine, such as Franz Alexander (1891–1964) and Helen Flanders Dunbar (1902–59), for example, were not only exploring the impact of emotions and personality on mental and physical health during this period but also, like Selye, regularly describing health and disease in terms of energy, stability, homeostasis, the balance of the nervous and endocrine systems, and adjustment to shock.[32] There were also close similarities between the temporality of Dunbar's "delayed-action mines of childhood," in which an initial shock or persistent conflict eventually caused psychological or physical collapse, and the pattern of Selye's general adaptation syndrome.[33] Interactions between Selye's studies and those of Dunbar, Alexander, and others may have been direct. There is certainly some evidence for an exchange of concepts and approaches between Selye and proponents of psychosomatic medicine: not only did Selye publish his reflections on psychosomatic processes in *Psychosomatic Medicine*, a journal founded and initially edited by Alexander and Dunbar, but, as one of the pioneers of psychosocial medicine in Britain, James Lorimer Halliday (1897–1983), pointed out in 1950, the range of chronic "diseases of adaptation or stress diseases" explored by Selye closely matched the psychosomatic diseases studied by Alexander and his colleagues.[34]

Although Selye tended to emphasize the manner in which the general adaptation syndrome emerged relatively unproblematically from his own experimental observations and clinical experience, it is evident that he mobilized a range of concepts circulating within scientific and medical debates about health and disease during the interwar years. Preoccupations with the limits of human adaptability to the stresses and strains of modern life, concerns about the psychological and physical impact of shock and fatigue, physiological studies of adaptive self-regulation, and clinical interest in the psychosomatic determinants of health collectively provided motivation and resources for Selye's formulation of the relationship between adaptation and disease. Much of Selye's subsequent research effort focused not on charting the impact of the mind or environment on physical health, however, but on identifying the biochemical mediators involved in adaptive reactions to stress.

Steroids and Stress

Similarities between the general adaptation syndrome and physiological studies of adaptive responses to environmental stresses should not disguise evident differences between Selye's work and those of his scientific predecessors and peers. First, Selye's sense of temporality clearly differed from

earlier work on shock and emergency reactions. His notion of an alarm reaction shared much in common with Cannon's account of fight or flight responses to danger, but Selye's discussion of the subsequent stages of resistance and exhaustion introduced an element of chronicity that was generally missing from previous studies. Although Cannon had referred to the impact of prolonged emotional disturbances, it was Selye's work primarily that foregrounded the pathological consequences of continued physiological attempts to adapt to relentless environmental stresses. Second, in focusing on chronicity Selye emphasized the role of hormones released from the adrenal cortex rather than those produced by the adrenal medulla. Thus, while Cannon and others investigated the contribution of adrenaline and noradrenaline to emergency reactions, Selye's research became increasingly concerned with the physiological actions of cortical steroids and their regulation by pituitary hormones.[35]

Selye's fixation with steroids, which emerged from his early studies of adrenal pathology, is evident in the diversity of the research projects that he coordinated, first at McGill and subsequently at the University of Montreal. During the early 1940s the range of projects supervised by Selye and funded by government agencies, charitable organizations, and pharmaceutical companies included investigations of the anesthetic properties of steroids, attempts to synthesize new "steroid compounds of probable pharmacological interest," work on the prevention of exhaustion following shock, experiments aimed at clarifying the actions of steroids on growth and renal function, studies on the role of steroids in oncogenesis, and inquiries into the interrelation between sex hormones.[36] Selye also possessed a prodigious capacity to convert the fruits of his "steroid research program" into published articles.[37] Between his arrival at McGill in 1933 and his departure in 1945, Selye authored or coauthored approximately three hundred academic papers, many of which offered original insights into the mechanisms of physiological adaptation, the physiology of sex hormones, and the functional biochemistry of cortical steroid hormones.[38]

In 1943 Selye published arguably his most substantial contribution to the field of steroid biochemistry, a four-volume *Encyclopedia of Endocrinology* that was dedicated to providing a "classified index of the steroid hormones and related compounds." Noting the lack of a convenient handbook for investigators working in a rapidly expanding field, Selye indicated that the purpose of the encyclopedia was to promote research by providing a classification of steroids according to their "most important chemical, physical and pharmacological properties." Selye's approach to the 728 steroids already identified was comprehensive and orderly. Starting with the simplest hydrocarbon nucleus, norestrane, the volumes proceeded through the parent compounds and their substitution products, providing space for entries relating to the isolation of the steroids from normal and pathological tissues; details

of their structure, synthesis, melting points, and optical rotation; comments on their pharmacological activities; details of any derivatives; and a list of reference numbers linking individual entries to the bibliography. Selye's introduction to the encyclopedia also revealed a sophisticated approach to the functional interrelations of steroid hormones, compatible with his formulation of the integrated endocrine control of adaptive stability. Although he admitted that the complex chemistry, as well as the wide range and often unpredictable combination of pharmacological actions, of steroid molecules tended to "give the impression of complete lack of orderliness," Selye insisted that the successful synthesis of many hormones and the results of ongoing research would continue to reveal logical functional correlations.[39]

According to Selye, steroids possessed a combination of independent and subordinate activities. Depending on the endocrine gland, whose function they primarily imitated, the independent actions of steroid hormones included folliculoid, testoid, luteoid, corticoid, gonadotropic, renotropic, antifolliculoid, and anesthetic activities. Each independent action was also associated with a number of subordinate actions generated by the hormone's effect on a variety of other target glands or metabolic processes. Reflecting his own research interests in adrenal function under stress, Selye cited the vital significance of the adrenocorticoid hormones as a prime example of this dual capacity: "Similarly among the corticoids some compounds have a particularly pronounced effect on sugar and others on salt metabolism, but all the corticoids exert a beneficial effect on life maintenance after adrenal deprivation. Hence both the sugar and the salt metabolism influencing activities are subordinate to the life-maintaining potency of the corticoids."[40]

While the main volumes of Selye's *Encyclopedia of Endocrinology* capture the state (and reveal the limits) of scientific knowledge about individual steroids, the "synoptic charts" detailing the naturally occurring steroid hormones that had been isolated from different tissues along with their pharmacological properties, as well as the bibliography, testify to the range of laboratory and clinical studies being pursued into the structure and function of steroids around the world.[41] Drawing on his expansive knowledge of the field, much of Selye's subsequent work during the 1940s focused on refining scientific understanding of the role of steroid hormones in health and disease. Arguing that hormones were produced for the "sole purpose of directing, regulating and coordinating the activities of the organism," he insisted that the objective of endocrinology was not the treatment of rare glandular diseases but the management of more common "hormonal derangements resulting from maladaptation to stress." Steroid hormones lay at the heart of the body's capacity to adapt to the stress of life: "not only sex," he wrote in 1949, "but the development and metabolism of the entire body, as well as its resistance and adaptability to exposure and disease, are influenced by the steroid hormones of the gonads, the adrenal cortex and the placenta."[42]

As his publications on endocrinology make clear, stress occupied an increasingly pivotal position in Selye's scheme of hormonal adaptation and resistance. Not only was it stress that initiated the chain of reactions leading, under certain conditions, to disease but individual glands and their hormonal secretions were understood primarily in terms of their involvement in homeostatic adjustments to stressful circumstances. From this perspective the corticoid hormones were "indispensable for the maintenance of life and especially for the acquisition of adaptation to changes in the external or internal environment of the body": patients suffering from adrenal insufficiency were advised to "take special care to avoid stress and strain," such as exposure to cold and excessive exercise. For Selye, adrenal function was subject to higher control: recent investigations had revealed "evidence that one of the most important physiologic roles of the anterior-lobe [of the pituitary gland] is concerned with adaptation to various types of non-specific stress" and that derangements of "the pituitary response to stress" constituted one of the causes of the diseases of adaptation.[43] During the postwar years Selye and his colleagues continued to explore the correlation between adrenal and pituitary function by investigating the physiological actions of adrenocorticotrophic hormone in shaping resistance to stress.[44]

Although most of Selye's work focused on the isolation of cortical and pituitary hormones and the identification of their physiological and pathological functions in animals subjected to stress, he was aware of the human implications of endocrine research, often speculating about the potential application of his work to a broad range of clinical problems. For other researchers and pharmaceutical companies, the clinical and financial benefits of chemical analysis of steroids were more directly relevant. Organotherapy with crude glandular extracts had become unfashionable, but awareness of the potential for certain steroids to reduce inflammation in patients with rheumatoid arthritis and allergies helped to mobilize funds and to coordinate research on the isolation and synthesis of active hormone preparations. One of the principal outcomes of these activities has been well covered by historians: in 1949 the American physician Philip S. Hench (1896–1965) and his colleagues announced the successful treatment of arthritis with a hormone, initially referred to as Compound E and subsequently named cortisone, that had been isolated from the adrenal cortex by the chemist Edward C. Kendall (1886–1972). In 1950 Hench, Kendall, and the Swiss chemist Tadeus Reichstein (1897–1996) were jointly awarded the Nobel Prize in Physiology or Medicine for their contributions to the discovery of the role of cortisone in the treatment of rheumatism.[45]

The focus of Hench and his colleagues on rheumatoid arthritis should perhaps have aligned their work closely with that of Selye, since rheumatism was commonly regarded, not just by Selye, as a "breakdown of the body's adaptive response to external stresses such as cold."[46] However, although

the three Nobel laureates referred to the publications of many physiologists and biochemists in their Nobel lectures, none of them cited Selye, who was also nominated for a Nobel Prize that year.[47] It may well be that Selye's preoccupation with stress and adaptation in animals distanced him from other researchers who were applying biochemical analyses of steroid compounds directly to the treatment of human diseases in this period. In addition, as we shall see, resistance to his ideas about adrenopituitary control of endocrine function may have been stimulated by growing skepticism about the theoretical viability of the general adaptation syndrome. In 1951, for example, Kendall directly dismissed "the adaptation syndrome of Selye" as an explanation for the influence of cortisone on health and disease.[48]

Kendall's curt rejection of Selye's work should not be taken to suggest that Selye was peripheral to the fields of steroid chemistry and endocrinology during this period. As both internal endorsements of his reputation by colleagues at McGill and nominations for the Nobel Prize suggest, he was highly regarded by scholars around the world. According to Roger Guillemin, who had been one of Selye's research fellows and who later received the Nobel Prize for his isolation of hypothalamic-releasing factors, Selye was "one of the major ferments of modern endocrinology."[49] The Argentinean physiologist Bernardo A. Houssay (1887–1971), who was awarded the Nobel Prize in 1947 for his discovery of the role of anterior pituitary hormones in sugar metabolism, similarly suggested that Selye possessed "exceptional and probably unique conditions and abilities" that enabled him to "dominate all aspects of endocrinology with equal competence"; in addition to owning the "largest endocrinological library in the world," commanding many languages, and being a "brilliant teacher," Selye possessed "a personal knowledge of the major part of experimental endocrinology" and had contributed "important original studies, executed with skilful technique, to the development of the science."[50] In Houssay's words, Selye's *Textbook of Endocrinology* was a volume of "historic importance, since it is the most complete synthesis of endocrinological facts published up to date."[51]

Selye's research on steroids also attracted interest from other quarters. As Kendall pointed out in his Nobel lecture, the exigencies of war had played a crucial part in stimulating research into pharmacologically active steroids in the United States.[52] Military interest in cortical hormone preparations was related in part to their potential to reduce mental and physical fatigue. The ability of cortical extracts and purified steroids to counteract the lassitude associated with adrenal insufficiency or to improve health and stamina among overworked and anxious populations had been highlighted during the 1930s and early 1940s, leading to a commercial market for the manufacturers of hormonal extracts such as Adreno-Spermin, which promised to reverse glandular imbalances generated by stress.[53] As the stress of combat became apparent during World War II, allied military commanders on both

sides of the Atlantic turned to laboratory studies of cortical steroids in the hope that the results would enable military physicians to identify and more effectively treat service personnel suffering from stress-induced fatigue.

Like shell shock and flying stress during World War I, cases of war neurosis among soldiers who had broken down "under the stress of active-service conditions" during World War II were explained primarily in terms of the fatigue and fear associated with prolonged engagement in hostile conditions.[54] In addition, psychosomatic symptoms among civilians subjected to intensive air raids were regarded as the product of anxieties precipitated by war: "It is to the war as a whole," wrote Aubrey Lewis (1900–75) in 1942, "with its accumulated stresses, that people have to adjust themselves, and signs of failure to do this can be taken as warning signals of neurosis."[55] As Selye pointed out in 1943, many of these studies of wartime illness supported his account of the general adaptation syndrome. The increased incidence of perforated peptic ulcers among British populations subjected to air raids, for example, could be explained in terms of an adrenocortical defense reaction, comparable to that produced in animals "by exposure to stress."[56] However, wartime studies of stress were only rarely linked directly to Selye's account of adaptation and disease. Although some military doctors described various stages of stress in a manner that echoed the features of Selye's triphasic general adaptation syndrome, they more often referred explicitly to Cannon's notion of alarm. According to the authors of a survey of anxiety states in the navy, for example, the "immediate stress of danger" provoked a "physiological adrenal-sympathetic response," comparable to Cannon's fight or flight reaction. If the pressures of combat persisted, this stage of "early stress" was followed (as in Selye's adaptation syndrome) by a phase of "established tension," which in turn led to a state of "anxiety with exhaustion."[57]

Although Selye's syndrome was often bypassed in this way, his work on adrenocortical steroids did shape military approaches to identifying and minimizing combat stress. After World War I the US Armed Forces had introduced a psychological screening program on the grounds that constitution determined resilience under stress. However, evidence that many supposedly stable recruits suffered from incapacitating fear and fatigue suggested that anyone could suffer from a breakdown depending on the duration and intensity of the stress to which they were exposed. Emotional casualties were thus regarded as inevitable products of war rather than as examples of lack of courage or malingering.[58] According to Roy R. Grinker (1900–1993) and John P. Spiegel (1911–91), who conducted an extensive investigation into the effects of stress on American air force personnel, the "stress of war tries men as no other test that they have encountered in civilized life." "Under sufficient stress," they continued, "any individual may show failure of adaptation, evidenced by neurotic symptoms."[59] Among British forces a different

ethos prevailed. While their American counterparts emphasized environmental stress, British military authorities tended to prioritize constitutional factors: pilots who failed to cope with the demands of warfare and threatened operational efficiency were deemed to be deficient in character and, if found guilty of a "lack of moral fibre," could be returned to a basic grade or discharged.[60]

One of the challenges facing military authorities in relation to the selection of recruits and the identification of stress-related disorders was that psychological assessment was based primarily on subjective reporting of symptoms and behavior. Research carried out by the physiologists Gregory Pincus (1903–67) and Hudson Hoagland (1899–1982), however, suggested that an alternative strategy might be available, one that combined Selye's physiological studies of the role of the adrenal cortex in resisting stress with measurements of the urinary excretion of steroid metabolites. Drawing on Selye's work on histological changes in the adrenal cortex after exposure to stress and on evidence that the excretion of 17-ketosteroids increased during illness, Pincus and Hoagland investigated whether the output of 17-ketosteroids might serve as a marker of physiological stress in aircraft personnel. The results indicated that both urinary volume and the concentration of 17-ketosteroids increased when men were flying or subjected to fatiguing activities comparable to those encountered on long flights. Moreover, it appeared that while "poorer performers tended to exhibit the greatest ketosteroiduria and diuresis," pilots who were more resistant to stress-related fatigue tended to excrete "low amounts of 17-ketosteroids, as if the stress of daily living exerts little drain upon their adrenal cortex secretion."[61]

As Hoagland suggested, the results of these experiments offered not only a means of measuring physiological stress more accurately and identifying those who were less capable of resistance but also the possibility of developing a strategy for "preventing the stresses of flight from interfering too greatly with our homeostatic mechanisms."[62] Given that an individual's capacity to endure fatiguing ordeals appeared to be related to adrenal function, Pincus and Hoagland attempted to determine whether certain steroids increased resistance to stress. Although they emphasized that efficacy appeared to depend, at least to some extent, on individual motivation and the degree of stress, their studies indicated that pregnenolone in particular was effective in "counteracting psychomotor fatigue," as measured by urinary 17-ketosteroid excretion.[63] The work of Pincus and Hoagland was significant not only because it established a physiological marker for stress, one that did much to confirm Selye's emphasis on adrenocortical mediation of the stress response, but also because it provided an opportunity to circumvent industrial measures of fatigue that emphasized only productivity or performance.[64] Steroid chemistry thus promised a solution to the problems of occupational stress and nervous fatigue that clinicians, patients, industrial

managers, and military authorities, as well as experimental physiologists, had been seeking since the late nineteenth century.

The originality of Selye's approach to the role of steroid hormones in adapting to chronic stress is arguably evidenced by the skeptical reception that it initially provoked from other scholars in the field, particularly Cannon. According to Selye, Cannon's resistance appeared to revolve around four of Selye's "basic tenets": the importance of chronic, rather than merely acute, responses; the central role of the adrenal cortex and pituitary gland; the nonspecific nature of adaptive responses; and the manner in which "the most diverse diseases can result from stress, depending upon the simultaneous influence of different conditioning agents."[65] In addition, Cannon may have been unimpressed by the crudity of some of Selye's experimental work. In 1922 Cannon had criticized studies that measured organ responses only in terms of size or that drew conclusions from the application of injuries, such as organ ablation, that could not be considered physiological.[66] Although Selye did include more sophisticated histological evidence, much of his early work on the effects of prolonged stress used organ weight as an indicator of physiological reaction. In spite of doubts about his methods and theories, however, Selye's theory of adaptation and disease and his emphasis on the role of steroid hormones in mediating stress reactions began to attract scientific and clinical attention because of its potential to address the rising tide of chronic disease that was threatening to submerge modern societies.

Stress and Disease

Just as Selye liked to explain the origins of the general adaptation syndrome in terms of a smooth transition from laboratory experiment to theory, he also tended to highlight the relatively unproblematic conceptual journey from adaptation to stress. Although he acknowledged that there were objections to his terminology from the start, he claimed a relatively clear lineage for his growing preoccupations with stress: laboratory research provided the evidential basis for the general adaptation syndrome, which was itself transformed by further research and clinical observation into a fully fledged pathology of stress. Yet Selye's notion of the general adaptation syndrome and his conversion to the language of stress received mixed responses. In spite of his considerable efforts to establish the validity of the syndrome and to justify his formulation of stress, many scientists and clinicians remained skeptical.

Conflicting reactions to Selye's account of adaptation and stress are particularly evident in responses to his Heberden oration on stress and the general adaptation syndrome, delivered in London in June 1950.[67] By this

time Selye had moved from McGill University to establish the Institute of Experimental Medicine and Surgery at the University of Montreal. Selye's departure from McGill had been prompted by a number of factors, including increasingly strained relationships with senior colleagues, some of whom questioned the validity of Selye's work as well as the ethics of accepting sponsorship from the pharmaceutical sector without sufficient institutional control.[68] Internal disputes at McGill coincided with a generous offer from the University of Montreal, which at that time was not only investing in what Selye referred to as its "magnificent new campus" but also aiming to increase its recruitment of international researchers.[69] Following his arrival at the university in 1945, Selye rapidly established his institute as one of the prime locations for studying interactions between environmental circumstances, endocrine function, and health. It was from the institute, for example, that he began to publish his annual surveys of stress literature from 1950.[70]

Selye's relocation was accompanied by a significant shift in his approach to the language of disease. Prior to 1950 Selye had conceptualized pathology in terms of faulty adaptation to environmental circumstances; when he did use the term "stress," it signified merely the external trigger of adaptive responses.[71] This hierarchy of factors, in which stress operated only through adaptive processes, persisted, albeit in muted form, in his 1950 Heberden oration: "Stress acts only through the general adaptation syndrome," he insisted. But there are signs that Selye had begun to reconceptualize stress, referring to it not merely as an external trigger of internal processes but also as a physiological or pathological process itself. "In the biological sense," he argued in 1950, "stress is the interaction between damage and defence, just as in physics tension or pressure represents the interplay between a force and the resistance offered to it."[72] Perhaps recognizing the flexibility and fecundity of the concept, Selye increasingly employed the word "stress" rather than "adaptation" in both scholarly and popular accounts of his research. By 1956, when Selye published arguably his most influential study of the causes and pathogenesis of chronic disease, stress now took center place: in *The Stress of Life*, the general adaptation syndrome was only the visible manifestation of stress, which now constituted "the common denominator of all adaptive reactions in the body." More specifically, stress, rather than adaptation, signified the pivotal biological process at the heart of individual strategies for coping with modern life: "Stress," Selye insisted, "is essentially the rate of all the wear and tear caused by life."[73] To differentiate between the harmful agent and the biological response more clearly, Selye began to employ a new term, "stressor": "All agents can act as stressors, producing both stress and specific actions."[74]

Selye's formulation of the general adaptation syndrome and his linguistic shift toward stress generated heated debates in the *British Medical Journal* and the *Lancet*. A number of correspondents dismissed Selye's "bold attempt

at a monistic pathology." Having pointed out that Selye's latest contribution had left him "in some mental confusion," H. N. Green, for example, doubted whether "Professor Selye's more recent ideas, even born as they are out of prodigious labours, will survive, *in their present form*, for very long." In particular, Green was critical of Selye's extrapolation from studies of the pathological effects of large doses of steroids administered to rats on the one hand to an ambitious account of the role of corticoids in human disease on the other. A. P. Meiklejohn similarly disapproved of Selye's reliance on a number of unsubstantiated speculations. In one of the most hostile reactions to Selye's Heberden oration, Ffrangcon Roberts exposed what he regarded as fatal contradictions at the heart of Selye's scientific framework for understanding disease. Uncritical acceptance of Selye's conflicting definitions of stress, Roberts argued, could lead only to an uncomfortable paradox: "Therefore stress, in addition to being itself and the result of itself, is also the cause of itself."[75] Although they often recognized the heuristic value of Selye's reflections on the pathogenesis of chronic disease, subsequent correspondents reinforced this sense of skepticism, contesting Selye's claims that his focus on individual adjustment to stressful environments was original, challenging Selye's theoretical interpretation of laboratory data, and emphasizing the need for further research. "The whole problem is full of obscurities," an editorial complained in response to a further article by Selye the following year, "and alternative explanations of Professor Selye's results are likely to persist until much more experimental work has been done to separate out specific physiological effects from those of a nonspecific nature."[76]

Selye was exasperated by the tone of most of this correspondence, which he suggested had been written with "some animosity and little, if any, reference to facts," but he found considerable support from many other reviews of his work.[77] Selye's apparently "brilliant exposition of a most fascinating piece of research" in 1950 was initially well received by members of the Heberden Society, and according to one reviewer of Selye's first monograph on stress: "No-one has the right to pronounce judgment without carefully and critically reviewing the evidence, and no-one who reads this monumental contribution to the medical classics can fail to be profoundly impressed."[78] Selye's research continued to attract grants from state departments, charitable organizations, and pharmaceutical companies interested in the potential clinical applications of laboratory studies of stress, and many clinicians welcomed Selye's attempt to develop a novel theoretical framework for understanding a range of biological reactions and clinical manifestations that had previously resisted explanation. In 1952 the British surgeon David Le Vay applauded the manner in which Selye's "painstaking researches" helped to provide a "unitary conception of disease," integrating studies of the endocrine system with psychosomatic medicine and providing

insights into the pathogenesis of functional disorders such as peptic ulcer, fibrositis, rheumatoid arthritis, and asthma.[79] During the postwar decades the central features of Selye's triphasic adaptation syndrome, and particularly his focus on the role of the adrenopituitary system in regulating stress responses, were not only adopted by allergists, clinical ecologists, and psychiatrists treating patients but also discussed in the context of sociobiological studies of aggression, psychoanalytical accounts of pain and suffering, investigations into cyclical variations in mammalian populations, studies in occupational and military psychology, and in nascent politicized deliberations about the pursuit of happiness and health on both sides of the Atlantic.[80]

Selye's studies of adaptation, steroids, and stress also generated support within the Rockefeller Foundation. In January 1950 a monthly report to the trustees explored recent studies of the relationship between adrenal function and disease. According to John S. L. Browne (1904–84), a British scientist who had received a Rockefeller Award at McGill and who had been best man at Selye's first wedding, the general adaptation syndrome constituted "the new pool of Bethesda," an original "philosophical point of view which alters our concept of disease":

> It presents the picture of a basic pathological process at work which when it mounts to a certain magnitude is the disease. And this idea, I may add, is completely at variance with the older views of scientific medicine. It is at variance with the ideas of compartmentalized disease, which is the central dogma of modern medical practice. Medical men who recognize the revolutionary and shattering nature of these developments realize that a great adjustment in our thinking has to be made. Here is the pool of Bethesda.[81]

As many of the chapters in this volume demonstrate, Selye's influence extended well beyond the scientific academy. From the early 1950s through to the 1980s, his research on adaptation and stress was reported in national newspapers, magazines, and clinical journals across the world. *Time* magazine, for example, ran a number of cover stories on the multiple manifestations of stress in the lives of contemporary Americans, often focusing on Selye's theories.[82] Medical advice books written for a general audience also transmitted Selye's message to the world. In 1956 *Healthy Minds and Bodies*, intending to provide British families with guidance on "all medical, marriage and motherhood problems," cited Selye's research on the bodily impact of stress to reinforce the book's promotion of preventative health care: "Professor Selye's conclusion to date is that stress is an important factor in the causing of all physical diseases, except, of course, those due to injury, infection or poisoning. This, as you can see, is a very forcible reminder that Worry Can Kill."[83] The uptake of Selye's ideas was facilitated by his deliberate attempts to advertise his work to a global audience. In addition to delivering lectures around the world, Selye published a number of best-selling books on stress

and disease, many of which not only set out his scientific theories in laymen's terms but also established his own historical narrative of the discovery and demonstration of the general adaptation syndrome.[84] Although his scientific credibility was not universally endorsed by his peers, it was partly through Selye's popularizing zeal that stress came to be regarded as a cause of chronic disease in the decades following World War II.

Historicizing Selye

Retrospective assessments of the place and importance of Selye's work on adaptation and stress, like those expressed at the time, have been mixed. As researchers increasingly turned to clinical studies of human disease and to investigations of the psychological mediators of stress, such as appraisal and coping, Selye's experimental model, in which laboratory rats were stressed by starvation, extreme temperatures, and excessive exercise, appeared anachronistic and unethical. In 1970 an English physician, John Todd, for example, dismissed the general adaptation syndrome as one of "the errors of medicine." "Imperfections in this general-adaptation process," he wrote, "were thought to be a major cause of many maladies, notably much arterial disease and rheumatoid arthritis. Although many of Selye's observations were valuable, few now accept this theory." Fifteen years later, Paul Christian and Fernando Lolas were even more emphatic in their rejection of Selye's place in modern accounts of adaptation, stress, and disease. Although they acknowledged that the general adaptation syndrome had provided a valid model for understanding the effects of some stressors, they insisted that Selye's notions no longer fit the new "theoretical pathology" that supposedly provided the "conceptual foundation of medicine": "The Selyean concept, the original idea of the pituitary-adrenal humoral axis," they argued, "was abandoned and was no longer at the center of the discussion."[85]

Selye's detractors were only partially correct. While competing formulations of stress tended to marginalize Selye's biological focus, his emphasis on the neurohormonal mediators of adaptation and stress continued to inform medical and scientific publications as well as popular accounts of ill-health. For many clinicians and scientists Selye's notion of "diseases of adaptation," his analysis of the role of steroid hormones in mediating resistance to stress, and his promotion of stress as a novel language of disease remained paradigmatic.[86] In 1976 the British psychiatrist Richard Mackarness (1916–96) insisted that Selye would "come to rank with Louis Pasteur, Frederick Banting and Alexander Fleming among the immortals of medical research" for his role in clarifying the "mechanics of adaptation and the body's response to the threats to its stability." Two years later, Tom Cox, a prominent British occupational psychologist, similarly lauded Selye's contributions to modern

understandings of stress: the capacity for the concept of stress to constructively bring together "fragments of information and relatively isolated ideas from a variety of different areas," he suggested, owed much to "the pioneering writing of Hans Selye." Many of Selye's students were also profoundly influenced by his vision and personality, and some of them, such as Roger Guillemin, made major contributions to the science of hormonal regulation and stress. In a tribute to Selye published three years after his death, a number of students and colleagues testified to his enduring impact on the field. According to Claude Fortier (1921–86), Selye was "one of the rare giants of contemporary biology," blessed with intuition, intellectual depth, and remarkable energy. As Guillemin pointed out in a more balanced evaluation of Selye's work, Selye "was the source of many ideas which, whether accepted or, more often, challenged; whether confirmed as such or eventually profoundly modified, were at the roots of modern neuroendocrinology."[87]

Measured historical reflection is needed to reconcile conflicting accounts of Selye's place in the modern history of stress. Scholarship should resort neither to uncritical adulation of his achievements nor to premature dismissal of his contributions to the field. Rather, it should aim to investigate fully the origins, development, and reception of his work within scientific, social, and cultural contexts. This chapter has attempted to extend the process of historical reconstruction. Whether embraced or discarded, Selye's formulation of adaptation and disease provided an important conceptual matrix for subsequent discussions of the mechanisms and manifestations of stress reactions, serving at the same time to fertilize research into the bio-psycho-social determinants and the pathophysiological pathways of chronic disease well into the twenty-first century. For this reason, careful study of Selye's changing approaches to stress offers a constructive window onto shifting debates about the impact of environmental circumstances on physiological regulation, individual health, and social harmony. Indeed, in many ways, Selye's journey from the physiology of shock and adaptation to the biochemistry of stress and the psychology of happiness exemplifies the complex history of modern stress research.

Notes

I am grateful to the Wellcome Trust for funding the research on which this article is based, to David Cantor and Ed Ramsden for their editorial support and comments, and to the participants in the conference at which this paper was first presented.

Epigraphs: J. S. L. Browne, "The New Pool of Bethesda," confidential monthly report to the trustees, January 1950, Rockefeller Foundation Archives, Rockefeller Archive Center, Sleepy Hollow, New York, 16; and John W. Todd, "Plain Words in Medicine," *Lancet*, June 13, 1964, 1287.

1. Hans Selye, "A Syndrome Produced by Diverse Nocuous Agents," *Nature* 138 (July 4, 1936): 32.

2. Hans Selye, *The Stress of My Life* (Toronto: McClelland and Stewart, 1977), 85.

3. Ibid., 71–72, 68–69; italics in the original.

4. John W. Mason, "A Historical View of the Stress Field," part 1, *Journal of Human Stress* 1 (1975): 6.

5. François-Joachim Beer, "L'histoire du concept biologique du stress," *Histoires des Sciences Medicales* 11 (1977): 135–40; Georgette Goupil, *Hans Selye: La sagesse du stress* (Quebec: Nouvelle Optique, 1981); Russell Viner, "Putting Stress in Life: Hans Selye and the Making of Stress Theory," *Social Studies of Science* 29, no. 3 (1999): 391–410.

6. See the Nomination Database for the Nobel Prize, *The Official Website of the Nobel Prize*, accessed September 17, 2013, http://nobelprize.org/nobel_prizes/medicine/nomination/nomination.php?string+Hans+Selye.

7. For a detailed discussion of Selye's work and its influence, see Mark Jackson, *The Age of Stress: Science and the Search for Stability* (Oxford: Oxford University Press, 2013).

8. Biographical studies and personal reminiscences include Beer, "L'histoire"; Goupil, *Hans Selye*; Andrée Yanacopoulo, *Hans Selye ou la cathédrale du stress* (Quebec: Le Jour, 1992); Paul Rosch, "Remembering Hans Selye and the Birth of 'Stress,'" *Health and Stress* 1 (2010): 1–14; and Istvan Berczi, "Stress and Disease: The Contributions of Hans Selye to Neuroimmune Biology," http://home.cc.umanitoba.ca/~berczii/page2.htm, accessed September 16, 2013. More critical historical evaluations of Selye's work include Viner, "Putting Stress in Life"; Cary L. Cooper and Philip Dewe, *Stress: A Brief History* (Malden, MA: Blackwell, 2004); Anne Harrington, *The Cure Within: A History of Mind-Body Medicine* (New York: Norton, 2008); Lea Haller, "Stress, Cortison und Homöostase: Künstliche Nebennierenrindenhormone und physiologisches Gleichgewicht, 1936–1960," *NTM Zeitschrift für Geschichte der Wissenschaften, Technik und Medizin* 18 (2010): 169–95; Serge Doublet, *The Stress Myth* (Sydney: Ispilon, 2000); Angela Patmore, *The Truth about Stress* (London: Atlantic Books, 2006); and Robert Kugelmann, *Stress: The Nature and History of Engineered Grief* (Westport, CT: Praeger, 1992).

9. Hans Selye and Thomas McKeown, "Studies on the Physiology of the Maternal Placenta in the Rat," *Proceedings of the Royal Society of London* 119 (1935): 1–31.

10. Selye, "Syndrome Produced," 32.

11. Hans Selye, "Studies on Adaptation," *Endocrinology* 21 (1937): 169–88; Selye, "The Significance of the Adrenals for Adaptation," *Science* 85 (1937): 247–48; Selye, "Adaptation Energy," *Nature*, suppl. no. 141 (1938): 926; Selye, "Experimental Evidence Supporting the Conception of 'Adaptation Energy,'" *American Journal of Physiology* 123 (1938): 758–65; Selye, "The Prevention of Adrenalin Lung Edema by the Alarm Reaction," *American Journal of Physiology* 122, no. 2 (1938): 347–51.

12. Selye, "Experimental Evidence."

13. Hans Selye, *The Story of the Adaptation Syndrome* (Montreal: Acta, 1952), 50–51.

14. On the citation and impact of Selye's article in the *Journal of Endocrinology*, see Eugene Garfield, "Citation Indexes for Science: A New Dimension in Documentation through Association of Ideas," *Science* 122 (1955): 108–11.

15. Hans Selye, "The General Adaptation Syndrome and the Diseases of Adaptation," *Journal of Clinical Endocrinology* 6, no. 2 (1946): 119, 131.

16. Francis G. Crookshank, "Science and Health," in *Science and Civilization*, ed. Francis S. Marvin (London: Oxford University Press, 1923), 247.

17. Ibid., 248. See also W. Langdon Brown, "The Return to Aesculapius," *Lancet* 2 (1933): 821–22; and Lord Horder, *Health and a Day* (London: Dent, 1937), 5–6.

18. John Eric Erichson, *On Railway and Other Injuries of the Nervous System* (Philadelphia: Lea, 1867). See also Ralph Harrington, "The Railway Journey and the Neuroses of Modernity," in *Pathologies of Travel*, ed. Richard Wrigley and George Revill (Amsterdam: Rodopi, 2000), 229–59; Nicholas Daly, "Railway Novels: Sensation Fiction and the Modernization of the Senses," *ELH* 66 (1999): 461–87; Daly, "Blood on the Tracks: Sensation Drama, the Railway, and the Dark Face of Modernity," *Victorian Studies* 42 (1998): 47–76; George M. Beard, *American Nervousness: Its Causes and Consequences* (New York: Putnam's Sons, 1881); Alfred Lief, ed., *The Common Sense Psychiatry of Adolf Meyer* (New York: McGraw-Hill, 1948); and Rhodri Hayward, "Medicine and the Mind," in *The Oxford Handbook of the History of Medicine*, ed. Mark Jackson (Oxford: Oxford University Press, 2011), 524–42.

19. For discussion of concerns about the "pathology of progress," see Charles E. Rosenberg, "Pathologies of Progress: The Idea of Civilization as Risk," *Bulletin of the History of Medicine* 72 (1998): 714–30.

20. Roberta Bivins, *Alternative Medicine? A History* (Oxford: Oxford University Press, 2007), 79.

21. Advertisement for Phyllosan, *Times*, January 30, 1934, 11; George W. Crile, *The Origin and Nature of the Emotions* (1915; repr., Charleston, SC: Bibliobazaar, 2006), 38; George W. Crile, *A Physical Interpretation of Shock, Exhaustion and Restoration* (London, Hodder and Stoughton, 1921).

22. Crile, *Origin and Nature*, 127–28, 121, 127–28, 100–101, 107–8, 127.

23. Anson Rabinbach, *The Human Motor: Energy, Fatigue and the Origins of Modernity* (Berkeley: University of California Press, 1992); William James, "The Energies of Men," *Science* 25 (1907): 326; *Report of the War Office Committee of Enquiry into "Shell-Shock"* (London: HMSO, 1922), 55–56.

24. James L. Birley, "Goulstonian Lectures on the Principles of Medical Science as Applied to Military Aviation," *Lancet*, May 29, 1920, 1147–51. Birley cited the psychological studies of Sigmund Freud and W. H. R. Rivers and the physiological investigations of Walter Cannon.

25. Carleton B. Chapman, "The Long Reach of Harvard's Fatigue Laboratory, 1926–47," *Perspectives in Biology and Medicine* 34 (1990): 17–33; Steven M. Horvath and Elizabeth C. Horvath, *The Harvard Fatigue Laboratory: Its History and Contributions* (Englewood Cliffs, NJ: Prentice Hall, 1973).

26. The role of nervous or psychological stability was embedded in psychoanalytical accounts of mental health and in debates about shell shock; see Sigmund Freud, *Beyond the Pleasure Principle and Other Writings*, trans. John Reddick (London: Penguin, 2003), 43–102; Nigel Walker, "Freud and Homeostasis," *British Journal for the Philosophy of Science* 7 (1956): 61–72; *War Office Committee*, 13, 95–96.

27. Walter B. Cannon, "Organization for Physiological Homeostasis," *Physiological Reviews* 9 (1929): 399–431; Cannon, *The Wisdom of the Body* (New York: Norton, 1932); Cannon, "Some Conditions Controlling Internal Secretion," *Journal of the American Medical Association* 79 (1922): 92–95; Cannon, "New Evidence for Sympathetic Control of Some Internal Secretions," *American Journal of Psychiatry* 79 (1922): 15–30.

28. Cannon, "New Evidence," 27; Cannon, "Some Conditions," 95.

29. Selye contributed to discussions of homeostasis and heterostasis in Chandler MacCuskey Brooks, Kiyomi Koizumi, and James O. Pinkston, eds., *The Life and Contributions of Walter Bradford Cannon, 1871–1945* (New York: SUNY Downstate Medical Center, 1975), 89–112.

30. Walter B. Cannon, "Stresses and Strains of Homeostasis," *American Journal of the Medical Sciences* 189 (1935): 1–14; Walter B. Cannon, "The Role of Emotion in Disease," *Annals of Internal Medicine* 9 (1936): 1453–65.

31. Mark Jackson, "The Pursuit of Happiness: The Social and Scientific Origins of Hans Selye's Natural Philosophy of Life," *History of the Human Sciences* 25 (2012): 13–29.

32. Franz Alexander, *Fundamentals of Psychoanalysis* (1949; repr., London: Allen and Unwin, 1960), 35–39; Helen Flanders Dunbar, *Mind and Body: Psychosomatic Medicine* (New York: Random House, 1947), viii, 4, 10. Alexander also used the term "stress" to describe emotional conflicts leading to organic disturbances; see "Psychological Aspects of Medicine," *Psychosomatic Medicine* 1 (1939): 7–18.

33. Dunbar, *Mind and Body*, 17–25.

34. Hans Selye and Claude Fortier, "Adaptive Reaction to Stress," *Psychosomatic Medicine* 12 (1950): 149–57; James L. Halliday, "Significance of the Discovery of the Effects of Cortisone," *Lancet* 256 (1950): 365–66. In *Stress without Distress* (New York: Signet, 1975), Selye included works by Alexander and Dunbar in the bibliography. Selye also included a chapter on the psychosomatic implications of his work in *The Stress of Life* (New York: McGraw-Hill, 1956), 260–72. The article by Selye and Fortier, "Adaptive Reaction to Stress," in *Psychosomatic Medicine*, also suggests reciprocal familiarity between Selye, Dunbar, and Alexander.

35. Hans Selye and Christiane Dosne, "The Action of Desoxycorticosterone Acetate and Progesterone on the Blood and Tissue Chlorides of Normal and Adrenalectomized Animals," *American Journal of Physiology* 132 (1941): 522–28; Claude Fortier and Hans Selye, "Adrenocorticotrophic Effect of Stress after Severance of the Hypothalamo-Hypophyseal Pathways," *American Journal of Physiology* 159 (1949): 433–39. In distinguishing between medullary and cortical hormones, Selye also developed innovative surgical techniques (to remove the adrenal medulla without damaging the cortex, for example, or to remove the pituitary gland) that were adopted by other researchers; see Selye, "Thymus and Adrenals in the Response of the Organism to Injuries and Intoxications," *British Journal of Experimental Pathology* 17 (1936): 234–48; and Gerald Evans, "The Adrenal Cortex and Endogenous Carbohydrate Formation," *American Journal of Physiology* 114 (1935): 297–308.

36. Hans Selye to F. Cyril James, May 31, 1943, file 38/30/81, RG 38, c. 6, McGill University Archives, Montreal (hereafter cited as MUA); Letters and research reports in file 2720, RG 2, c. 99, MUA. In 1943 Selye received a total of $40,310 from charitable, state, and pharmaceutical businesses, with a further $36,520 already promised for the following year; see file 38/30/81, RG 38, c. 6, MUA.

37. Hans Selye to Dr. H. A. Lambert, August 4, 1944, file 38/30/81, RG 38, c. 6, MUA.

38. Hans Selye and Christiane Dosne, "Effect of Cortin after Partial and after Complete Hepatectomy," *American Journal of Physiology* 128 (1940): 729–35. A full list of Selye's publications, including more than 1,400 articles and 22 monographs, was

compiled to support his nomination to the Canadian Medical Hall of Fame. I am grateful to Dr. Milagros Salas-Prato for a copy of the dossier.

39. Hans Selye, *Encyclopedia of Endocrinology*, vols. 1–4 (Montreal: Franks, 1943), 1:1, 7. Two volumes on the ovary were published three years later. For a similar discussion of the chemistry and physiology of steroid hormones, see Hans Selye, *Textbook of Endocrinology*, 2nd ed. (Montreal: Acta Endrocrinologica, 1949), 47–85.

40. Selye, *Encyclopedia of Endocrinology*, 1:8.

41. Ibid., 4:10–48.

42. Selye, *Textbook of Endocrinology*, 11–13, 50.

43. Ibid., 160, 199.

44. Hans Selye and Helen Stone, *On the Experimental Morphology of the Adrenal Cortex* (Springfield, IL: Charles C. Thomas, 1950), 95–99.

45. Harry M. Marks, "Cortisone, 1949: A Year in the Political Life of a Drug," *Bulletin of the History of Medicine* 66 (1992): 419–39; David Cantor, "Cortisone and the Politics of Empire: Imperialism and British Medicine, 1918–1955," *Bulletin of the History of Medicine* 67 (1993): 463–93; Nicolas Rasmussen, "Steroids in Arms: Science, Government, Industry, and the Hormones of the Adrenal Cortex in the United States, 1930–1950," *Medical History* 46, no. 3 (2002): 299–324; Jean-Paul Gaudillière, "Better Prepared Than Synthesized: Adolf Butendandt, Schering Ag and the Transformation of Sex Steroids into Drugs (1930–1946)," *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 612–44; Viviane Quirke, "Making British Cortisone: Glaxo and the Development of Corticosteroids in Britain in the 1950s–1960s," *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 645–74.

46. Cantor, "Cortisone," 466.

47. Edward C. Kendall, "The Development of Cortisone as a Therapeutic Agent," in *Nobel Lectures, Physiology or Medicine, 1942–1962* (Amsterdam: Elsevier, 1964), 270–88; Tadeus Reichstein, "Chemistry of the Adrenal Cortex Hormones," in *Nobel Lectures*, 289–308; Philip S. Hench, "The Reversibility of Certain Rheumatic and Nonrheumatic Conditions by the Use of Cortisone or of the Pituitary Adrenocorticotropic Hormone," in *Nobel Lectures*, 311–41.

48. Edward C. Kendall, "The Adrenal Cortex and Rheumatoid Arthritis," *British Medical Journal*, December 1, 1951, 1295–99.

49. Roger Guillemin, "A Personal Reminiscence of Hans Selye," *Experientia* 41 (1985): 560–61.

50. Selye's library contained approximately 150,000 reprints in 1943. See Jenny Kalsner, "The Unique Stress Library of Dr. Hans Selye," *Canadian Medical Association Journal* 129 (1983): 288–89; and Selye, *Encyclopedia of Endocrinology*, 1:1.

51. Bernardo A. Houssay, preface to Selye, *Textbook of Endocrinology*, xii–xiii.

52. Kendall, "Development of Cortisone," 271–72.

53. Rasmussen, "Steroids in Arms," 306–9. For a contemporary study of steroids and performance in animals, see Dwight J. Ingle, "Work Performance of Adrenalectomized Rats Treated with 11-Desoxycorticosterone Sodium Phosphate and 11-Desoxy-17-Hydroxycorticosterone," *American Journal of Physiology* 133 (1941): 676–78.

54. William Sargant and Eliot Slater, "Acute War Neuroses," *Lancet*, July 6, 1940, 1–2; Gilbert Debenham, William Sargant, Denis Hill, and Eliot Slater, "Treatment of War Neurosis," *Lancet*, January 25, 1941, 107–9.

55. Aubrey Lewis, "Incidence of Neurosis in England under War Conditions," *Lancet*, August 15, 1942, 183. For the context surrounding Lewis's report, see Stephen T. Casper, "The Origins of the Anglo-American Research Alliance and the Incidence of Civilian Neuroses in Second World War Britain," *Medical History* 52 (2008): 327–46. For other contemporary studies of combat stress, see David Stafford-Clark, "Aspects of War Medicine in the R.A.F.," *British Medical Journal*, January 30, 1943, 139–40; G. V. Stephenson and Kenneth Cameron, "Anxiety States in the Navy: A Clinical Survey and Impression," *British Medical Journal*, November 13, 1943, 603–7; Charles P. Symonds, "The Human Response to Flying Stress," *British Medical Journal*, December 4, 1943, 703–6; Symonds, "The Human Response to Flying Stress," *British Medical Journal*, December 11, 1943, 740–44; and David Stafford-Clark, "Morale and Flying Experience: Results of a Wartime Study," *Journal of Mental Science* 95 (1949): 10–50.

56. Hans Selye, "Perforated Peptic Ulcer during Air-Raid," *Lancet*, February 20, 1943, 252.

57. Stephenson and Cameron, "Anxiety States," 604.

58. Mark K. Wells, *Courage and Air Warfare: The Allied Aircrew Experience in the Second World War* (London: Cass, 1995), 77–81.

59. Roy R. Grinker and John P. Spiegel, *Men under Stress* (Philadelphia: Blakiston, 1945), vii.

60. Wells, *Courage and Air Warfare*, 186–208.

61. Gregory Pincus and Hudson Hoagland, "Steroid Excretion and the Stress of Flying," *Journal of Aviation Medicine* 14 (1943): 173–93. Although Pincus and Hoagland did not cite Selye in this paper, they subsequently became aware of his work after Selye contributed a chapter to a volume on hormones edited by Pincus; see Hans Selye, "Hypertension as a Disease of Adaptation," in *Recent Progress in Hormone Research*, vol. 3, ed. Gregory Pincus (New York: Academic Press, 1948), 343–61.

62. Hudson Hoagland, "Adventures in Biological Engineering," *Science* 100 (1944): 64.

63. Ibid., 67.

64. William Gomberg, "Measuring the Fatigue Factor," *Industrial and Labor Relations Review* 1 (1947): 80–93.

65. Selye, *Stress of My Life*, 73–74, 221–22. Selye also reflected on Cannon's reluctance to endorse his ideas at a conference in San Diego in 1978. I am grateful to Dr. David Fernandez, who collaborated with Selye in the 1970s and 1980s, for a recording of Selye's presentation to the conference and for copies of his correspondence with Selye.

66. Cannon, "Some Conditions," 94.

67. Hans Selye, "Stress and the General Adaptation Syndrome," *British Medical Journal*, June 17, 1950, 1383–92.

68. Letters and memoranda relating to Selye's work and the move to the University of Montreal are in RG 38 c. 6, file 30/38/80, 1933–46; RG 2, c. 99, file 2720, 1938–45; RG 2, c. 99, file 2721, 1944–45, MUA.

69. Selye, *Stress of My Life*, 100.

70. Hans Selye, *The Physiology and Pathology of Exposure to Stress: A Treatise Based on the Concepts of the General-Adaptation-Syndrome and the Diseases of Adaptation* (Montreal:

Acta, 1950); Hans Selye, *Annual Report on Stress* (Montreal: Acta, 1951); Hans Selye and Alexander Horava, *Second Annual Report on Stress* (Montreal: Acta, 1952).

71. Selye's application of stress and adaptation in this way echoed general usage. In 1945, in their study of the behavior of American air force pilots in combat situations, *Men under Stress*, Grinker and Spiegel argued that "under sufficient stress any individual may show failure of adaptation" (vii). Physiologists employed stress in a similar way to denote environmental factors that caused demonstrable changes in endocrine function; see Robert H. Williams, Herbert Jaffe, and Carol Kemp, "Effect of Severe Stress upon Thyroid Function," *American Journal of Physiology* 159 (1949): 291–97.

72. Selye, "Stress," 1392, 1384.

73. Selye, *Stress of Life* (1956), 54, viii. By the 1976 edition of the same book, stress was defined in even more fundamental terms as "the nonspecific response of the body to any demand"; see Hans Selye, *The Stress of Life* (New York: McGraw-Hill, 1976), 74.

74. Selye, "Stress," 1392.

75. H. N. Green, "Stress and the General Adaptation Syndrome," *British Medical Journal*, July 22, 1950, 215; A. P. Meiklejohn, "General Adaptation Syndrome," *British Medical Journal*, July 15, 1950, 164; Ffrangcon Roberts, "Stress and the General Adaptation Syndrome," *British Medical Journal*, July 8, 1950, 104–5.

76. G. S. W. Evans, letter, *British Medical Journal*, July 8, 1950, 105–6; "Diseases of Maladaptation," *British Medical Journal*, February 10, 1951, 285–86; Selye's article was published in the same issue; see Hans Selye, "Role of Somatotrophic Hormone in the Production of Malignant Nephrosclerosis, Periarteritis Nodosa, and Hypertensive Disease," *British Medical Journal*, February 10, 1951, 263–70. For other comments on Selye's approach, see "The General Adaptation Syndrome," *British Medical Journal*, June 17, 1950, 1410–11; A. Wesley Hill, "The General Adaptation Syndrome," *British Medical Journal*, July 22, 1950, 220; "Diseases of Adaptation," *Lancet*, June 10, 1950, 1078; George W. Pickering, "Significance of the Discovery of the Effects of Cortisone on Rheumatoid Arthritis," *Lancet*, July 15, 1950, 81–84; Ernst Jokl, "Adaptation in Physiological Processes," *Lancet*, December 2, 1950, 705–6.

77. Hans Selye, "Diseases of Maladaptation," *British Medical Journal*, March 3, 1951, 472–73.

78. "Rheumatic Diseases as Diseases of Adaptation: Professor Hans Selye's Heberden Oration," *British Medical Journal*, June 10, 1950, 1362–64; "What Is Stress?," *Lancet*, February 3, 1951, 279.

79. David Le Vay, "Hans Selye and a Unitary Conception of Disease," *British Journal for the Philosophy of Science* 3 (1952): 157–68.

80. Mark Jackson, *Allergy: The History of a Modern Malady* (London: Reaktion Books, 2006), 203–4; John J. Christian, "The Adreno-Pituitary System and Population Cycles in Mammals," *Journal of Mammology* 31 (1950): 247–59; John R. Clarke, "The General Adaptation Syndrome in the Study of Animal Populations," *British Journal for the Philosophy of Science* 3 (1953): 350–52; David Bakan, *Disease, Pain, and Sacrifice: Toward a Psychology of Suffering* (Chicago: University of Chicago Press, 1968); Edward O. Wilson, *Sociobiology: The New Synthesis* (1975; repr., Cambridge, MA: Belknap, 2000), 242–55.

81. Selye, *Stress of My Life*, illustration, 143; John S. L. Brown "The New Pool of Bethesda," confidential monthly report to the trustees, January 1950, Rockefeller Foundation Archives, Rockefeller Archive Center, Sleepy Hollow, New York, 16.

82. "Medicine: The Life of Stress," *Time* 56 (October 9, 1950): 93–94; "Medicine: Three-Letter Wonder," *Time* (April 16, 1951); "Medicine: Stress and Strain," *Time* 63 (January 18, 1954): 66; "Medicine: Chain of Strain?," *Time* (January 31, 1955); "Medicine: Life and Stress," *Time* (December 3, 1956); "Research: How to Handle Stress; Learn to Enjoy It," *Time* (November 29, 1963); Claudia Wallis, "Stress: Can We Cope?," *Time* (June 6, 1983): 49–54—all accessed July 10, 2009, http://www.time.com/time/magazine.

83. T. Traherne and Frank Preston, eds., *Healthy Minds and Bodies* (London: Waverley Book Company, 1956), 10.

84. Selye, *Story*; Selye, *Stress without Distress.*

85. John W. Todd, "The Errors of Medicine," *Lancet*, March 28, 1970, 665–70; Paul Christian and Fernando Lolas, "The Stress Concept as a Problem for a 'Theoretical Pathology,'" *Social Science and Medicine* 21 (1985): 1363–65.

86. Paul J. Rosch, "Stress and Cancer: A Disease of Adaptation?," in *Cancer, Stress and Death*, ed. Jean Tache, Hans Selye, and Stacey B. Day (New York: Plenum, 1979), 187–212; Angelo A. Alonso, "Health as Situational Adaptation: A Social Psychological Perspective," *Social Science and Medicine* 21 (1985): 1341–44.

87. Richard Mackarness, *Not All in the Mind* (London: Pan Books, 1976), 47; Tom Cox, *Stress* (London: Macmillan, 1978), 174; Claude Fortier, "A Giant of Biology," *Experientia* 41 (1985): 561–62; Guillemin, "Personal Reminiscence," 561.