NUTRIENTS, STRESS, AND MEDICAL DISORDERS
Nutrition & Health

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NUTRIENTS, STRESS, AND MEDICAL DISORDERS

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Series Editor’s Introduction

The Nutrition and Health Series of books have had great success because each volume has the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science; (2) timely, in-depth reviews by the leading researchers in their respective fields; (3) extensive, up-to-date fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overlap of information between chapters, but targeted, interchapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient/health professionals’ questions that are based on the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research- and practice-oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Nutrients, Stress, and Medical Disorders, edited by Shlomo Yehuda and David I. Mostofsky, is a critical addition to the Nutrition and Health Series and fully exemplifies the goals of the series. Stress, health, and illness are well accepted as intimately linked. However, the critical influence of nutritional status (and/or specific dietary components that can affect the brain) on mental functions affected by stress has often been a neglected area of research focus. This volume has been developed to examine the current clinical findings and put these into historic perspective as well as point the way to future research opportunities. Both editors are internationally recognized leaders in the field of nutrition and neurological function. Both are excellent communicators and they have worked tirelessly to develop a book that is destined to be the benchmark in the field because of its extensive, in-depth chapters covering the most important aspects of the complex interactions between diet and its nutrient components, mental health, stress, and its impact on disease states. The introductory chapters provide readers with the basics so that the more clinically related chapters can be easily understood. The editors have chosen 40 of the most well-recognized and respected authors from around the world to contribute the 25 informative chapters in the volume.

The chapters of Nutrients, Stress, and Medical Disorders are logically organized to provide the reader with a basic understanding as well as an appreciation of the develop-
ment of the field of stress research, its relationship to brain function, and the potential for nutrients to affect these variables. The first section reviews the history, methodologies, and basic scientific information that is essential to understanding the following sections. In Chapter 1, the reader is introduced to the leading investigators who developed the area of clinical stress research. Three scientific disciplines are compared: biology—exemplified by the work of Walter B. Cannon and Hans Selye; psychology—Kurt Lewin and Richard Lazarus; and psychobiology—John W. Mason and coworkers. In every experimental field of research, the animal models used have been crucial in understanding the complexities of the disease states as well as the development of drugs to treat the disease. Equally important is the understanding of the potential for nutrients to affect responses to stress and/or its treatment. Chapter 2 provides an in-depth look at the animal models used in stress research, effects of food and its deprivation, and also critiques the model’s value in predicting human responses. Chapter 3 introduces the reader to the complexities of the physiological responses to stress in the brain, nervous, and endocrine systems, and also includes detailed information about the differences in responses between males and females. Chapter 4 begins the integration of nutrition, stress, and disease. The chapter includes a summary of the extensive literature that is finding a strong association between diets containing fruits and vegetables that are rich in polyphenolic compounds with antioxidant functions and reduced risks of diseases often associated with aging that affect the brain such as Alzheimer’s and Parkinson’s diseases. The importance of the blood–brain barrier and its role in stressful situations is discussed in-depth in Chapter 5. This chapter also includes an analysis of the roles of neuroactive amino acids and their interactions with the blood–brain barrier.

The second section of the volume includes chapters addressing the interactions between specific nutrients, effects of food, and stress. The editors and their colleagues have included an extensive chapter on the effects of fatty acids on stress responses. Both editors of this volume and Dr. Norman Salem have collaborated on another book in this series, Fatty Acids, and consequently, these dietary components are of special interest to the chapter authors. Chapter 6 provides relevant information on the mechanisms of actions of the major polyunsaturated long-chain fatty acids, their availability in the food supply, and their actions on the nervous system, with emphasis on their effects during stress. Chapter 7 examines the interactions between stress, glucocorticoids, and the brain. This chapter spans the research from the cellular to the behavioral levels, as well as providing information on genetic influences on stress responses that are organized in a comprehensive table. Herbal product use has increased dramatically over the last decade and in the United States, these products are classified as dietary supplements. The chapter on herbal products, stress, and the mind critically reviews the clinical literature and provides guidance to health professionals concerning the efficacy and safety of St. John’s Wort, Kavakava, valerian, ginkgo and several other plant products associated with stress reduction. Chapter 9 compares and contrasts the stress reactions to drug cravings vs food cravings. Chapter 10 specifically examines the effects of alcohol and alcoholism on stress to the individual, family members, the fetus, and the neonate. Of interest are the interactions between environmental influences other than diet and the effects on stress and central nervous system (CNS) functions. These influences include the effects of temporal (rise in obesity incidence, increase in the number of women in the workforce) and space
(neighborhood, city, state, and the medical benefits available) on the interactions between diet and stress.

The chapters in the third section of *Nutrients, Stress, and Medical Disorders* examine the health, mental health, and cognitive functions influenced by stress. Beginning with the discussion of the developing fetus in Chapter 12, there is an extensive review of the literature that points to the critical effects of maternal nutritional status as well as stress level on fetal physical and mental development. Certain components of the diet have specific function in the CNS and are critical for mental health. Chapter 13 examines the role of lipids in the development and treatment of depression. The exciting preliminary data indicate that eicosapentaenoic acid has beneficial effects in depressive patients as well as having virtually none of the serious side effects seen with current drug therapies. To further examine depression, Chapter 14 reviews the role of nicotine in depression as well as sleep. Chapter 15 looks at the clinical data that point to a role of fish oils, rather than any specific long-chain fatty acid, on neurological responses that may lead to the development of aggressive behaviors. Another area given a great deal of public interest is obesity. The next chapter reviews the studies that have looked at the consequences of obesity on stress and the development of eating disorders. This chapter examines the effects of eating on reducing anxiety and its potential to further increase the obesity epidemic.

The fourth and final section of *Nutrients, Stress, and Medical Disorders* reviews the effects of stress on chronic disorders and the influence of inflammation on diet, dietary components, neurological functions, disease incidence, and cognitive functions. Several of these chapters review novel findings, such as those seen in Chapter 17, which examines the adverse effects of hypercholesterolemia on immune cells and their functions. To assure that readers understand the effects of high-circulating cholesterol levels on disease, there is an extensive review of the role of cholesterol in immune cell membranes and cytokines. Huntington’s disease is an inherited neurodegenerative disease that progresses fairly rapidly, leaving the patient with many physical as well as behavioral abnormalities. Until fairly recently, there were no treatments available; however, as described in the Chapter 18, it appears that there are preliminary findings that eicosapentaenoic acid may slow the progression of this disease. Another critical area that has been included in this unique volume is the effects of and major causes of stress in women. The major diseases that affect women at significantly higher rates than men include several autoimmune diseases, depression, and osteoporosis. All of these medical conditions are discussed in detail in Chapter 19. Also included in this chapter are discussions of stressors associated with menstruation, including polycystic ovarian syndrome and premenstrual syndrome. Type 2 diabetes is a major chronic disease and is preceded by a syndrome that is linked to insulin resistance, syndrome X. The next chapter looks at the role of fatty acids in the development of insulin resistance as well as syndrome X and the stress this metabolic syndrome places on the individual. Another chapter with novel findings deals with the roles of specific amino acids on mental functions. Chapter 21 reviews the effects of amino acids on sleep, mood, and responses to stress. Cardiac function is acutely as well as chronically affected by stress. Less well known is the importance of certain nutrients (such as carnitine, coenzyme Q, and thiamine) on cardiac muscle and nerve responses. The new data on the nutritional requirements that may be increased in the injured or
stressed heart are described in Chapter 21. Chapter 22 describes how brain functions are also often adversely affected by stress and the resulting inflammation of brain cells. Long-chain fatty acids are abundant in brain tissue and their dietary intake level has been associated with modulating complex inflammatory responses of specific cytokines in distinct areas in the brain. The next chapter continues to examine the effects of inflammation in the brain and its effects on memory functions. This chapter describes the development of memory, distinct areas of the brain and cytokines that are associated with memory, and the balance between the importance of inflammatory molecules for the development of some memories and the adverse effects of certain inflammatory mediators on memory, especially with stress and aging. The final chapter examines the complex interactions between inflammation and diet throughout the life cycle. This full-circle analysis of the major consequences of stress, dietary deficiencies, and genetic predisposition reminds us of the critical role of nutrition in modulating responses to stress-induced inflammation.

Hallmarks of all of the chapters include complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. There are more than 20 relevant tables, and 55 useful figures, as well as more than 2000 up-to-date references; all chapters begin with a Key Points section, and close with a conclusion that provides the highlights of major findings. The volume contains a highly annotated index and within chapters, readers are referred to relevant information in other chapters.

This important reference text provides practical, data-driven integrated resources based on the totality of the evidence to help the reader evaluate the critical role of nutrition, especially in at-risk populations, in optimizing health and preventing stress-related chronic illnesses. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of foods and nutrients that are routinely consumed and how these help to maintain mental as well as physical health.

In conclusion, Nutrients, Stress, and Medical Disorders, edited by Drs. Yehuda and Mostofsky, provides health professionals in many areas of research and practice with the most up-to-date, well-referenced, and easy-to-understand volume on the importance of nutrition in reducing stress-related chronic diseases and optimizing health. This volume will serve the reader as the benchmark in this complex area of interrelationships between diet, specific nutrients, CNS function, immune responses, and mental health. The editors are applauded for their efforts to develop the most authoritative resource in the field to date and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, PhD, FACN
Series Editor
Preface

The entry of the 21st century has been accompanied by a continuing surge of interest in brain science that began with the "Decade of the Brain" initiative. The laboratory research and clinical practice that followed have contributed to a realignment of perspectives, an integration of theory and thought, and the establishment of numerous multidisciplinary collaborations. Nutrition has begun to be recognized for its pharmacological relevance and stress phenomena are no longer viewed simply as mental health constructs. The study and treatment of health and illness has become the province of a broad segment of scientists and clinicians that includes psychologists, immunologists, biochemists, and public health professionals along with physician specialists from medicine. Even a cursory scanning of the published literature reveals the vast terrain that such enterprises represent. Journals, edited volumes, and monograph publications from almost all related disciplines can be expected to report on developments that cross the once familiar disciplinary boundaries. Investigations of nutrition, behavior, and health—in all their combinations—are now more the rule than the exception. For whatever reasons this has come to be, it has taken hold. The implications for research direction inherent in such activities, and especially the potential for interventions and treatments of many serious health conditions, are profound and are attracting the attention of the entire community of health science and delivery.

In *Nutrients, Stress, and Medical Disorders* we have assembled a sampling of the issues and findings that are representative of much of the current theoretical and laboratory activity. The volume is addressed to professionals and graduate students from diverse areas, for whom the need to become better informed about concepts and methodologies from neighboring disciplines is not readily solved by the specialized scientific literature. We have attempted to provide a wide-ranging collection of chapters by established experts that will provide a useful introduction to the literature of each of the areas of stress, nutrition, and medical disorders. In doing so, we have left it to the individual reader to attempt the global integration of the various messages that are presented, and to extract the salient features that will allow extensions for future scientific investigations or clinical applications. We are most appreciative of the valuable support of Humana Press in bringing this work to publication. We are especially grateful to Paul Dolgert, Editorial Director and to Andrianne Bendich, Series Editor for their expertise and patience in working with us on this project, as well as the earlier volumes that we have prepared. Although we were not able to include all of the relevant topics nor include chapters by all of the available experts, it is our hope that the efforts of the respective authors will merit a favorable reception by the audience of those who are advancing our knowledge in each of these areas—nutrition, stress, and health—so that our boundaries of scientific knowledge will be extended and that the quality of human life will be improved.

*Shlomo Yehuda, PhD*

*David I. Mostofsky, PhD*
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I

HISTORY, METHODOLOGY,
AND BASIC SCIENCE
Stress Revisited
A Methodological and Conceptual History

Martha M. Faraday

KEY POINTS

• The modern concept of stress developed over the last 150 yr in two separate branches of science: biology and psychology.
• Because biology and psychology historically are informed by different philosophical traditions with regard to the purpose of science, the concepts of stress that emerged from these two streams are quite different.
• The philosophical differences between biology and psychology dictate the methodological and statistical tools employed by each group of scientists—and therefore shape how questions are asked and answered.
• In the late 20th century, scientists with a psychobiological orientation have attempted to bridge these gaps, drawing on the strengths of both disciplines.
• Better understanding of the relationship between stress, health, and disease and of factors that protect or make the individual vulnerable require integrated conceptual and methodological approaches.

1. INTRODUCTION

Threats or challenges to self precipitate a cascade of responses. The threat or challenge may be physical, environmental, social, or psychological. It may be anticipated, presently occurring, remembered, or imagined. It may be tangibly dangerous, symbolically threatening, or demanding of personal growth. Responses to threats and challenges also take on many forms, including psychological and biological reactions. Emotional life may be overcast by anxiety, and the presence of others sought for reassurance and reevaluation of the threat. Decisions about coping strategies are sifted, weighed, and implemented. The individual’s body and brain are steeped in powerful biochemicals. This process, in which internal or external events—stressors—threaten or challenge an organism’s existence and well-being and stress responses occur that are directed toward reducing the event’s impact, is stress (Baum, Gatchel, & Krantz, 1997; Baum, Grunberg, & Singer, 1982; Baum, Singer, & Baum, 1981).
This concept of stress captures the work of many different kinds of stress investigators, including those who regard organisms as primarily biological entities, those who regard organisms as primarily psychological entities, and, less commonly, those who regard organisms as psychobiological entities. These different theoretical orientations have resulted necessarily in different methodological approaches to understand stress, health, and disease. This divergence in approach is rooted in the historical emergence of stress research in which the biological and psychological streams developed largely in isolation from one another. These historical traditions are sufficiently powerful that the remarkable insights of early investigators as well as their errors of omission continue to be perpetuated methodologically and conceptually in today’s work. The hybrid psychobiological tradition is beginning to bridge this gap by conceptualizing health and disease as holistic states, recognizing that the subjective psychological world exists inseparable from the biological activities of the body and brain.

This historical and present-day methodological and conceptual divergence in the stress field also reflects a broader, more fundamental difference in point of view about the purpose of science and the tension between two apparently conflicting goals: the need to discover the laws that govern systems and the need to understand individual differences. This critical difference influences the formulation of scientific questions, how experiments are designed, and how data are collected and interpreted and has been described by Kurt Lewin as a conflict between the Aristotelian and Galilean modes of thought (Lewin, 1935).

Lewin notes that the Aristotelian approach assigned paramount importance to an object’s membership in a given class because the class itself defined the essence of the object (Lewin, 1935). Classes were dichotomous, mutually exclusive, and defined as the total of characteristics that the group of objects had in common. The laws of science consisted of events or behaviors that occurred frequently and without exception (Lewin, 1935). Importantly, in the Aristotelian conceptualization lawful events were distinct from chance events; chance events were not subject to scientific laws. Because Aristotelian lawfulness can only be demonstrated by frequency, laws implicitly have a statistical, probabilistic nature, and the individual per se not only disappears but is not susceptible to lawful explanation (Lewin, 1935).

In contrast, Galilean physics assumed that the entire physical world was comprehensibly lawful, that “[t]he same law govern[ed] the courses of the stars, the falling of stones, and the flight of birds” (Lewin, 1935, p. 10). Membership in a conceptual class as a criterion for understanding an object was irrelevant because the outward appearance of an object did not define its behavior. Mutually exclusive, antithetical categories also lacked meaning and were replaced with the concepts of gradations and series. The fact that an object behaved in a particular way frequently or only once also became irrelevant because laws describing the physical world applied regardless of observed frequency. The distinction between lawful events and chance events disappeared—both common and uncommon events were subject to laws.

The psychologist, generally speaking, is an Aristotelian. Phenomena must be manifested frequently and in groups of organisms in order to be studied meaningfully. Differences in how organisms respond to a manipulation constitute within-group error—the noise of individual differences. Organisms that respond in an extreme way to the manipulation may be considered outliers that bias the group mean. An experiment is successful
when probabilistic functions indicate that a group mean is unlikely to have occurred by chance if this group indeed belongs to a population that the control group is assumed to represent. For the psychologist, lawfulness and, by extension, truth, are frequency.

The biologist pursues truth as a Galilean. According to the Galilean point of view, all phenomena are governed by “strict exceptionless lawfulness” (Lewin, 1935, p. 23). The law and, by extension, the truth of a phenomenon can be demonstrated by the responses of one subject. Whether this subject’s responses are similar to other subjects’ responses makes no difference to the validity of the law. A consequence of this point of view is that there is no need to express subjects’ responses as a mean and apply statistical techniques. Each subject’s data stand validly alone as expression of particular laws; parametric manipulations blur the underlying laws and their interrelationships. For the biologist, truth is embodied in all observations.

This chapter differs from traditional reviews of the stress literature in several ways. First, in addition to describing the concepts of stress that emerged from each tradition, this review highlights conceptual omissions. Conceptual omissions are important because lines of research are driven by the perception of what is known and what is not known but would be worthwhile to know. Second, methodological inclusions and omissions also are identified. These inclusions and omissions are important because how experiments are designed, what is measured, who is measured, whether and how measurements are manipulated (e.g., statistical analyses), how measurements are interpreted, and how error is conceptualized together determine the nature of the truth that is discovered. The two streams of stress research historically have found different remedies to issues of design, measurement, interpretation, and error that flow from the Aristotelian vs Galilean distinction. These remedies persist today in ongoing work; each has limitations and advantages.

2. THE BIOLOGISTS

Walter B. Cannon’s classic work on the fight-or-flight response and Hans Selye’s influential conceptualization of stress in terms of the general adaptation syndrome (GAS) are the essence of the biological approach to stress. These investigators were central to early the definition of the stress concept as it related to health and illness, and their influence can be seen clearly today in the focus on the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis. To understand the context in which the biological tradition of stress research developed, however, one must first consider the methodological and conceptual approach of 19th-century physiologists. It is against this backdrop that the early 20th-century Cannon proposed that stress is an interaction between external or internal events and homeostatic capacities and the mid-20th-century Selye promulgated the concept that the stress response is nonspecific and occurs in the three stages of the GAS.

Two individuals are relevant. The methodological approach in which Cannon and Selye were trained was epitomized by the work of revered American physiologist William Beaumont. The rationale for this methodological approach was articulated by the great French physiologist Claude Bernard (1813–1866). Bernard’s theoretical approach and discoveries also laid the conceptual groundwork for Cannon’s contributions to the modern understanding of stress.
2.1. Biological Methodology: Inclusions and Omissions

The methodological hallmarks of the biological approach to the study of stress are: simple experimental designs that often are not fully factorial, one or two independent variables, and multiple control groups; use of small numbers of subjects; careful observation and description and meticulous quantitation of observations; and measurement of biological variables directly related to the question under study. Omissions include the lack of statistical description or analysis; complex experimental designs in which interactions as well as simple main effects can be examined; use of dependent variables such as behaviors that may indicate whether a biological change has behavioral relevance; explicit consideration of the possible role of individual differences such as subjects’ sex; and, generally, controls for psychological variables present in the experimental situation that may alter biological responses.

During the 19th century, physiologists were concerned about two kinds of error: error of measurement and error produced by individual differences among subjects. The error associated with individual differences might occur as a result of within-species biologically based differences but also might occur as a result of varying subject–environment interactions. These interactions included factors such as whether an animal was acclimated to the laboratory and its procedures. Because the measurement devices available to early investigators required reference to the whole animal or human as a check on their validity, factors affecting the whole subject were considered important sources of potential error. This 19th-century methodological approach is epitomized in William Beaumont’s work.

Beaumont, an Army physician stationed at Fort Crawford in the wilderness of early 19th-century Prairie du Chien, Wisconsin, cared for the French hunter Alexis St. Martin after a penetrating injury to the abdomen. As a result of the wound, St. Martin developed a permanent fistula through which the stomach lining and secretions could be observed (Beaumont, 1833). Beaumont worked with improvised equipment and without journals or colleagues. Nevertheless, he recorded many fundamental principles of digestive physiology. His discoveries included a stress-related fact well known today: extreme emotional states such as anger inhibit digestive activities. Beaumont’s work was proof that a single scientist working with meticulous care could reveal the laws of a phenomenon by observations made on one subject.

In contrast, by the late 20th century, biologists generally recognized only error of measurement. In part, this development is a consequence of biology’s ever-growing capacity for measurement. It is possible to measure the activity of a single cell, the opening and closing of a single receptor, the activation of chemical cascades linked to G protein receptors, the contents of one vesicle as it empties into a synapse, and particles down to the femtomole concentration. The measured responses cannot be observed directly; they are inferred from instruments and techniques. It is ironic that a scientific tradition grounded in the power of observation to reveal truth now uses instrumentation as a surrogate for observation. One consequence of measurement at a level remote from the whole organism is that the relevance of the whole organism and its environment has tended to disappear. As a result, although over 100 yr of investigations have revealed that subject–environment interactions can alter responses of biological systems, variables such as age, sex, housing conditions, and familiarity with being handled are not generally considered sources of potential error in modern biology.
Classically, statistical methods were also absent. Claude Bernard addressed the biologist’s aversion for statistics in his classic 1865 work *An Introduction to the Study of Experimental Medicine*. Bernard objected to the use of data analytical techniques for three reasons: their probabilistic nature obscured the individual, the use of statistics was inappropriate once a cause was defined, and mathematical manipulations that depended on probabilistic functions could never establish causality (Bernard, 1957). Bernard noted that disease outcomes depended on the age, sex, and temperament of the patient as well as on the disease process itself. The use of averages to express outcomes, therefore, could never inform the clinician about the future welfare of a particular patient, although mean outcomes might well describe the general phenomenon:

The results of statistics, even statistics of large numbers, seem indeed to show that some compensation in the variations of phenomena leads to a law; but as this compensation is indefinite, even the mathematicians confess that it can never teach us anything about any particular case; for they admit that if the red ball comes out fifty times in succession, that is no reason why a white ball would be more likely to come out the fifty-first time. (Bernard, 1957, p. 138)

According to Bernard, different experimental results, once measurement error had been controlled, were the result of variables in the experiment of which the investigator might not be aware. Determining why experiments thought to be similar produced different findings was, in Bernard’s view, the window of opportunity for making great discoveries about fundamental principles of biological systems.

### 2.2. The Biological Conceptualization of Stress: Inclusions and Omissions

Bernard’s influence also can be discerned in the biologic conceptualization of stress. He wrote about the instructive value of nonreplicating experiments to communicate a theoretical perspective about the underlying truths of biology: that processes that constituted and sustained life were no different from processes that accounted for changes in inanimate objects (Bernard, 1957). Both consist of chemical reactions that follow measurable laws. In framing physiological investigations this way, Bernard explicitly countered an older scientific tradition that, when confronted with individual differences in susceptibility to disease, assigned causality to differences in “vitality” in order to account for the discrepancies (Bernard, 1957). By putting physiology in a lawful context, Bernard also made clear that all processes operating in normal or diseased states were susceptible to scientific, biological explanation.

Bernard’s great contribution to the study of stress was his insight that an organism’s ability to move freely in the external environment depended on the capacity of its internal environment (le milieu interne) to buffer external influences. The more complex and stable the internal environment, the freer the organism was from fluctuations in the external world. A one-celled organism with a permeable membrane is at the mercy of environmental change. A plant can withstand environmental changes within limits but cannot remove itself from a hostile environment. Amphibians can remove themselves from a hostile environment but still are vulnerable to the temperature of their surroundings. Mammals, however, have developed to the point that they are largely free of the external environment, and humans have perfected this freedom. Because of the complexity
and stability of the human internal environment, humans are largely liberated from fluctuations in the external world. In Cannon’s words,

[...]

2.2.1. Walter B. Cannon

Bernard laid the groundwork for Cannon’s remarkable contributions to the study of stress. These contributions include that activity of the SNS could be provoked by internal manipulations or by external physical, environmental, or psychological events; that these homeostatic responses had evolutionary, adaptive, self-preserving significance; that the primary function of the SNS was to preserve homeostasis; and that stress could be conceptualized as an interaction between an organism and an external or internal event mediated by the processes of homeostasis.

Following in the tradition of Beaumont, Cannon’s early work focused on digestion using the then newly discovered X-ray technology to follow the course of food treated with bismuth (an X-ray-opaque substance) through the digestive tract. In experiments aimed at determining the purpose of stomach wall movements, Cannon observed that some animal subjects did not exhibit the characteristic waves. After reviewing the experimental methodology for errors in preparation and technique, the frustrated Cannon realized that the waves were absent only in animals that appeared distressed by the experimental procedure (Cannon, 1898, 1945). This observation led to a series of studies on other bodily changes provoked by strong emotions such as rage and fear and the capacity of the sympathetic nerves and adrenal medulla to enact these changes via adrenalin release (e.g., Cannon, 1914, 1928; Cannon & de la Paz, 1911).

At first these adrenalin-provoked changes appeared to be chaotic and disconnected responses of multiple body systems: blood sugar increased to the point of glycosuria; circulation was shunted preferentially to the heart, lungs, brain, and large muscles and markedly diminished to the other viscera; the digestive tract essentially ceased activity; clotting speed increased; and thresholds for muscular exhaustion increased. Cannon, however, was well acquainted with Darwin’s The Origin of Species. If one assumed that all of the changes had adaptive utility, then the apparent chaos resolved itself into a beautifully orchestrated response geared to the organism’s survival. In Cannon’s words,

[...]

The changes are, each one of them, directly serviceable in making the organism more efficient in the struggle which fear or rage or pain may involve; for fear and rage are aspects of organic preparations for action, and pain attends conditions which naturally evoke supreme exertion. And the organism which with the aid of increased adrenal secretion can best muster its energies, best call forth sugar to supply the laboring muscles, best lessen fatigue, and best send blood to the parts essential in the run or the fight for life, is most likely to survive. (Cannon, 1914, p. 270)
Further studies highlighted the importance of the sympathetic system in maintaining the various necessary steady states of the body (e.g., Cannon, 1929, 1932, 1933, 1935). The sympathetic system’s role was to keep the various bodily systems within narrow homeostatic boundaries in the face of challenges. When this process reached a point where the homeostatic system could no longer compensate, then homeostatic resistance was broken, the stress process became a “breaking strain,” and the organism was likely to suffer permanent injury, illness, or death (Cannon, 1935). Further, responses that were adaptive when the organism was confronted with a threat that may be physically fought or fled may well be destructive when the threat is not one that can be countered by physical action.

If the emotion is transformed into action, then the preparation is useful, and the body by anticipation is protected against a low blood sugar, an excessive heat, and a limiting shift in the direction of the acidity of the blood. If no action succeeds the excitement, however, and the emotional stress—even worry or anxiety—persists, then the bodily changes due to the stress are not a preparatory safeguard against disturbance of the fluid matrix but may be in themselves profoundly upsetting to the organism as a whole. (Cannon, 1933, p. 84)

What factors did Cannon omit? Other aspects of the stress concept that became the center of the psychological approach to stress (e.g., perception and appraisal) were also recorded in Cannon’s writings but were not examined systematically. Cannon clearly understood the importance of psychological influences, but his goal was the elucidation of the mechanisms by which physiological systems maintained the living organism. The idea that subjective processes influence the stress experience was not revisited experimentally for almost 50 yr, when John W. Mason emphasized the role of appraisal in the 1960s and 1970s, and Richard Lazarus made appraisal his theoretical centerpiece.

2.2.2. Hans Selye

Selye’s theory of stress is not only conceptually distinct from Cannon’s “fight-or-flight” response but specifically excludes homeostatic adjustments as stress responses. Selye’s influence on the field has been enormous. He was a proselytizer of stress, lecturing and writing extensively on his theory during a lengthy career, with more than 1500 scientific publications at his death. He also wrote several popular books on stress that were widely read.

Many different stimuli can raise heart rate—bounding up the stairs, worrying about finances, experiencing rage, joy, hope, or fear. To the extent that the heart rate increases regardless of the specific nature of the stimulus, the individual is experiencing stress according to Selye. Stress is the nonspecific response of the body to demands for adaptation—a deceptively simple concept that often has been misinterpreted to mean that responses to stressors are necessarily and by definition nonspecific. To grasp Selye’s conceptual structure, it is important to remember that he was trained as a physician.

In 1925, as a second-year medical student at the University of Prague, Selye observed that the process of diagnosing specific illnesses was complicated by the fact that many different diseases presented similarly (Selye, 1956/1976). Regardless of whether the sufferer endured scarlet fever or influenza, the patient was likely to report loss of appetite, diffuse pains in the joints, and fever and manifest an enlarged spleen or liver. So similar
were diverse disease manifestations that the art of the physician, Selye realized, depended on learning to discern subtle, specific, identifying symptoms against the broader nonspecific background of “the syndrome of just being sick” (Selye, 1956/1976). Ten years later, as a research assistant at McGill University, Selye thought he was on the trail of a new and important sex hormone. He attempted to identify the substance with a crude bioassay—injecting ovarian and placental extracts into rats and examining their organs for changes that were not known to be the result of identified sex hormones. His initial experiments yielded striking findings. Animals displayed a triad of symptoms: enlargement of the adrenal cortex; atrophy of the thymus, spleen, and lymph nodes; and deep, bleeding ulcers in the stomach lining (Selye, 1936). As the extracts were purified, however, their effects diminished. Selye realized that the triad was a response to the toxicity of the initial preparations. To test this hypothesis, he treated rats with formalin and other known irritating, toxic agents, and again the same triad was manifested (Selye, 1956/1976).

Selye reported that at this point he remembered the nonspecific “syndrome of just being sick” he had observed as a medical student (Selye, 1956/1976). He believed that this nonspecific syndrome was the key to understanding and treating commonalities among disease processes (Selye, 1956/1976). Continued experimentation revealed that the triad could be produced by multitudinous “stressors”—by injecting other biological substances and also by the use of physical agents such as cold, heat, X-rays, trauma, hemorrhage, pain, or forced exercise.

Further work was interpreted to indicate that this syndrome was manifested in three phases that Selye labeled the GAS: alarm, resistance, and exhaustion (Selye, 1936, 1946, 1956/1976). Initial exposure to the stressor—the alarm stage—resulted in production of adrenocorticotropic hormone (ACTH) by the pituitary which stimulated the adrenal cortices to produce corticoids. Later this model was modified to include the role of the hypothalamus and corticotropin-releasing factor (CRF) as instigators of the pituitary response (Selye, 1956/1976). The influence of the corticoids, Selye believed, produced the other distinguishing features of the triad—thymic involution and stomach ulcers. Other manifestations of the alarm stage included weight loss, hemoconcentration, and general tissue catabolism. If the stressor overwhelmed the body during this stage, the organism died. If the stressor did not overwhelm the body during this initial stage, then a period of adaptation to the presence of the stressor ensued—the resistance stage. In the resistance stage, production of corticoids dropped to only slightly above normal as the organism adapted to the stressor and body weight returned to normal. If the stressor continued long enough, however, the organism’s capacity for adaptation was overwhelmed and the stage of exhaustion ensued, in which corticoid production again rose and multiple “diseases of adaptation,” related to the destructive effects of continued excess corticoid production, might occur.

Over the next 40 yr, Selye’s original formulation of the concept of stress and the GAS evolved but remained consistent with his early ideas of a nonspecific syndrome in response to a specific stressor that also had specific, nonstress effects. In its most extensive articulation by Selye, stress is the nonspecific response of the body to any demand (pleasant or unpleasant) for adaptation (Selye, 1956, 1973). Stressors are specific stimuli that produce the nonspecific syndrome of stress (Selye, 1973). Stressor effects depend on the intensity of the demand made on the adaptive capacity of the body. Stress explicitly is not tension,
the discharge of hormones from the adrenal medulla, necessarily the result of damage, or any deviation from homeostasis. Further, stress is distinct from the stressor and also distinct from the GAS. Stress is “the state manifested by a specific syndrome which consists of all the nonspecifically induced changes within a biologic system” (Selye, 1956, p. 54). It is a construct whose existence can be inferred by the presence of specific indices.

Selye’s contention that stress is indexed by a nonspecific syndrome and occurs according to the GAS has been challenged by a number of investigators, including Mason (see Section 4). Criticisms of the nonspecificity tenet include that the same stressor does not produce the same syndrome across individuals. Selye counters in two ways. First, Selye noted that “conditioning” factors—internal (e.g., genetic predispositions, age, gender, past experience) or external (e.g., drug treatments, dietary factors, climate)—can enhance or inhibit the GAS, rendering individuals differentially susceptible to stress (Selye, 1975). Stimuli that demand adaptation have two kinds of action: stressor (nonspecific) effects (by definition the effects that produce stress) and specific effects. Specific effects are variable and characteristic of the individual agent. The organism’s response depends on both kinds of effects as well as on the organism’s reactivity.

Although best known for his emphasis on the corticosteroids, Selye’s model of stress effects as early as 1956 incorporated multiple organ systems. In addition to the HPA axis, it included the hypothalamic–pituitary–thyroid axis; the liver and its multiple metabolic functions; the kidneys, blood vessels, and connective tissues, and the immune system. Selye’s insight that stress potentially affected every bodily system was an important contribution to understanding how stress and disease states might be related.

What were Selye’s conceptual omissions? His model included every tissue in the body except for the brain. He speculated that corticoids might influence cognitive processes (Selye, 1976), but did not pursue this line of work. For Selye, the brain was primarily the anatomical locale for the hypothalamus and pituitary. In addition, despite his inclusion of individual differences in his model in the form of conditioning factors that mediate stress responses, his experimental work did not reflect a systematic attempt to model and manipulate conditioning factors. Further, although he knew that psychological stimuli were sufficient to evoke stress responses, he concentrated on physical and pharmacological stressors almost exclusively. Ironically, Selye’s parenthetical observation that psychological stimuli (which Selye considered mild in comparison to physical stressors) were sufficient to elicit such responses was one of the reasons Mason focused on psychological stress (Mason, 1971).

3. THE PSYCHOLOGISTS

Whereas biologists sought to understand the mechanisms by which the body responded to external or internal challenges, psychologists focused on the psychological apparatus through which events are sifted and experienced. The conceptual exemplar for the predominantly psychological approach to stress is Richard S. Lazarus, who emphasized appraisal, coping responses, and the process nature of the stress experience.

The methodological approach of experimental psychologists has a long and complex history in which the contributions of many individuals are relevant. Conceptually, the idea that the subjective psychological world constitutes the overwhelming reality for the individual and therefore can explain behavior was classically articulated by Kurt Lewin.
3.1. Psychological Methodology: Inclusions and Omissions

Experimental psychology and psychological field and epidemiological studies are predicated on the assumptions of Aristotelian science described by Lewin. For psychologists, truth is a probabilistic phenomenon, the validity of which is indicated by frequency of occurrence and the manifestation of which is assumed to follow a normal distribution. This probabilistic emphasis necessitates the use of groups of subjects, descriptive as well as inferential data analytical techniques, and, in theory, allows statements about a phenomenon only in terms of quantified uncertainty. The use of data analytical techniques allows complex multivariate (multiple independent variables as well as multiple dependent variables) experimental designs. With the tools of multivariate analysis and design, complex interrelationships among variables can be examined. The methodological hallmarks of the psychological approach to the study of stress also include measurement of psychological variables directly related to the phenomenon under investigation by self-report and, occasionally, measurement of behaviors and physiological responses. Error is assumed to be normally distributed, and random or quasi-random subject assignment is intended to optimize the probability that error is spread equally across treatment groups, allowing the treatment effect to stand out against the background of error.

Like early biologists, early experimental psychologists were aware of two kinds of error: error associated with measurements and individual difference error. As in biology, it is the treatment of individual difference error that has changed. Modern experimental psychology has largely overlooked the fact that statistical examination of individuals or very small groups is possible when subjects are measured repeatedly. As a result of the focus on group means as the unit of analysis, differences among subjects in the same group (within-group variance) are considered noise.

The general methodological approach of psychology is based on the work of many individuals from the 18th-20th centuries. That multicausal phenomena—ranging from reaction times to record a star’s movement across a stationary line in the eyepiece of a telescope to marriage, birth, and death rates in a country’s population—were more accurately described with many measurements rather than with a few was well-known in the 18th and 19th centuries. The work of Pierre S. Laplace (1749–1827) and Carl F. Gauss (1777–1855) in particular demonstrated that error is decreased when observations are combined and that patterns of error as well as patterns of data can be described with normal curves (Stigler, 1986). Many workers in the social sciences speculated that the curve also might have inferential utility. Adolphe Quetelet (1796–1874) struggled to use the curve as an inferential tool. In Quetelet’s words, “The greater the number of individuals observed, the more do individual peculiarities, whether physical or moral, become effaced, and allow the general facts to predominate, by which society exists and is preserved” (Quetelet, 1842, p. 6). One incontrovertible fact thwarted Quetelet: human behaviors were the complex outcome of multitudinous causes. Quetelet did not succeed in developing inferential statistical tools for the social sciences, but his work contributed to the insights of those who ultimately developed such tools: Sir Francis Galton, Francis Y. Edgeworth, Karl Pearson, and Ronald A. Fisher (Stigler, 1986).

As social scientists struggled with the complexity of large data sets, the psychophysicists found a way around the problem of multicausality in the context of experimental psychology. The powerful tool of the factorial design, a mainstay of modern psychology,
experimental psychology, emerged from Fechner’s work on the differential perceptual sensitivity of individuals. Like the social scientists of the time, Fechner knew that any given measurement was affected by a multitude of factors. From Gauss and Laplace he borrowed the assumption that patterns of error were normally distributed and applied the principle to the responses of a single subject. Fechner realized that these factors could be systematically manipulated and controlled by conducting experiments with many different conditions (Fechner, 1860). Herman Ebbinghaus took the next step in his studies of a more complex, multicausal phenomenon—memory—by using the normal distribution as a test for the validity of a set of data and casting departures from the central tendency in terms of their probable error. Modern statisticians have gone well beyond these insights, but the psychophysicists’ contributions of the factorial design to dissect causality and the applicability of the normal curve to inference were crucial to these later advances.

Methodologically, what was lost? Despite the fact that experimental psychology adopted the powerful tool of the factorial design that originated in psychophysics, the concept of the individual as a unit of study disappeared. Because early work focused on perceptual and cognitive properties of humans or on epidemiological and sociological outcomes, the use of animal models to study human conditions was not explored. Although Fechner in particular was aware that perceptual abilities were affected by factors such as whether the subject had recently eaten (Fechner, 1860), the idea that human behavior was a consequence of biological as well as psychological forces was not considered.

3.2. The Psychological Conceptualization of Stress: Inclusions and Omissions

Kurt Lewin focused on the role of the subjective psychological world in human experience—the cornerstone of appraisal, coping, predictability, and controllability. Lewin’s work has been chosen as the conceptual prelude to Richard S. Lazarus’s work because of Lazarus’s theme of subjective experience as crucial to understanding stress.

3.2.1. Kurt Lewin

In 1917, while serving in the German army during World War I, Lewin wrote a paper called “The War Landscape” in which he described how the soldier’s “life-space” is dramatically different from that of the civilian’s. A civilian might consider a secluded place as ideal for a picnic, whereas a soldier might consider the same place as likely to harbor an ambush (Hothersall, 1990). After the war Lewin continued to develop this theme into what became his theory of topological psychology, most extensively described in Principles of Topological Psychology (1936).

Lewin’s theory is centered on the concept of the life-space. The life-space constitutes the subjective psychological world of the individual. Within the life-space is a constantly changing complex of needs (innate states that involve tension, e.g., hunger) and quasi-needs (states that involve learned tensions, e.g., social acceptance or achievement). These tensions give rise to forces that are given direction (e.g., vectors) depending on the valence of particular goal regions. Any behavior could be explained, Lewin believed, by understanding the interrelationships among all of the operating vectors and goal regions in the “psychological field at that time” (Lewin, 1943, p. 294).
Lewin’s relevance to stress research is that the objective existence of an event in the external world is experienced by the individual within the subjective world of the life-space. Human reality is psychological, cognitive, objective, and fluid. Whether the event is a threat or challenge depends on how the event is perceived to impinge on the life-space. The subjective nature of the person–environment interaction is the essence of Lazarus’s work.

3.2.2. Richard S. Lazarus

“Psychological stress is a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being” (Lazarus & Folkman, 1984, p. 19). For Lazarus the subjective psychological experience of stress is a function of the psychological factors that the person brings to the transaction—past experiences, memories, biases, early childhood influences—and of the stimuli that the environment presents to the person. The implication of this definition is that individuals vary in the degree to which they experience stress in a particular situation and that objectively defined properties of the environmental stimulus are insufficient to explain the stress process.

According to Lazarus, two processes mediate the person–environment relationship: cognitive appraisal and coping. Appraisal is a process of evaluation in which it is determined to what extent a particular transaction or series of transactions between the person and the environment is stressful. Coping is the process through which the person–environment relationship demands and the emotions they generate are managed (Lazarus & Folkman, 1984).

Primary appraisal refers to the evaluation of a person–environment transaction as irrelevant, benign-positive, or stressful. The judgment that a transaction is irrelevant implies that nothing is to be lost or gained. A benign-positive transaction is one construed to enhance or potentially enhance well-being. The evaluation of a transaction as stressful indicates the possibility of harm/loss, threat, or challenge. When harm or loss is anticipated but has not yet occurred, the appraisal is one of threat and the resulting emotions are negative—fear, anxiety, or anger. The appraisal of challenge occurs when the transaction holds the potential for growth. The emotional responses to the challenge appraisal are positive—eagerness, excitement, and exhilaration (Lazarus & Folkman, 1984). Secondary appraisal involves assessing which coping options are available, how likely those options are to successfully address the problem, and to what extent the individual is able to carry out those options effectively.

The processes of appraisal are themselves modified by other factors within the person: commitments and beliefs. These variables exert influence on the appraisal process in three ways: (a) by determining what is salient for well-being in a given encounter, (b) by shaping the person’s understanding of the event and the resulting emotions and coping behaviors, and (c) by providing the basis for evaluating outcomes (Lazarus & Folkman, 1984). Situational factors also influence the stress experience. Lazarus and Folkman (1984) distinguish between uncertainty—the person not knowing what the event might mean—and ambiguity—lack of information about the situation itself. In ambiguous situations, factors about the person become the most important determinants of responses, and these factors also determine whether the ambiguity makes the experience more or less stressful. The processes of appraisal continue as the stressful transaction continues. This
process is called reappraisal and reflects the essential process nature of the stress experience.

Coping is the "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person" (Lazarus & Folkman, 1984, p. 141). Coping responses can be divided into two categories: responses aimed at the problem itself—problem-focused coping—and responses aimed at managing emotional responses to the problem—emotion-focused coping (Folkman & Lazarus, 1980). Problem-focused coping is more likely to occur when the situation is perceived to be susceptible to action, and emotion-focused coping is more likely when appraisal indicates that nothing can be done about the event. Problem-focused coping includes strategies such as defining the problem, looking for alternative solutions, weighing the costs and benefits of various alternatives, choosing among the solutions, and acting on the decision. Emotion-focused coping includes cognitive processes such as distancing, minimization, avoidance, and selective attention. These strategies may lead to reappraisal of the situation as less harmful than originally believed even though the situation remains objectively the same. Emotion-focused coping also consists of behaviors that may lead to reappraisals such as exercising in order to distract oneself from a problem, venting anger or fear, drinking alcohol, and seeking social support.

Omitted from the psychological model is the idea that humans also are complex biological organisms and that biological activity may affect psychological processes. Lazarus' work is driven by a one-way, top-down assumption—that cognition drives the stress experience including biological stress responses, and that biological responses, if they are relevant, are trivial compared to psychological processes. As a consequence, possible biological contributions to the subjective nature of the stress experience are not considered. It is possible, however, that appraisal and coping depend to some extent on the individual's biological responses during a given person-environment interaction. Lazarus left unexamined the possibility that people's cognitions are a coping response for their idiosyncratic physiological responses. In addition, because the subjective, psychological world is conceived of as a peculiarly human one, the possible role of animal models is not explored.

4. THE PSYCHOBIOLOGISTS

The psychobiologists' conceptual contributions to the understanding of stress integrate psychology and biology. John W. Mason is the prototypical stress psychobiologist. Mason's investigations are organized around two themes: that psychological stress is a potent inducer of stress responses and that the biological consequences of stress are homeostatic and depend on psychological factors. Biology's capacity for sensitive and accurate measurement of biological processes, its potential to illuminate underlying mechanisms governing diverse bodily systems, and its emphasis on the presence of lawful phenomena as revealed in the individual coupled with psychology's awareness of the power of environment and the subjective psychological world to influence behavior and the appropriate use of inferential statistics are united in Mason's 40 yr of investigations. The result is an approach to stress research that attempts to integrate the activity of multiple endocrine systems, cognitive variables such as appraisal, personality factors, and environmental or situational variables.
4.1. Psychobiological Methodology: Inclusions and Omissions

Methodologically, Mason’s work blends the biological and psychological traditions. In part, his work reflects the methodological emphases of the early physiologists—meticulous and repeated measurement of biological responses, small numbers of subjects and appreciation for the individual, and a disinclination to consider extreme responses as aberrant. He also draws from the psychological tradition, using field studies of soldiers during war to study human stress responses and creating animal models of psychological stress with classical and operant conditioning paradigms. Noting that means obscured individual differences in highly variable hormonal responses, he also used nonparametric tests and presented the data of individual human and animal subjects to demonstrate reported variability. He emphasized the need when examining hormonal responses to have repeated sampling and concurrent measurements of psychological states in order to interpret biological data (e.g., Mason, 1968c).

What did Mason omit methodologically? Missing from the human and animal work is measurement of behavior not directly related to the question under examination. In the animal work, this omission was partly a consequence of using conditioning paradigms in which the only behavior that could be measured in the experimental situation was lever-pressing. He also generally used only male subjects. Further, the stressors employed (e.g., exposure to war, 3-d avoidance task interfering with feeding and sleeping) were extreme.

4.2. The Psychobiological Conceptualization of Stress: Inclusions and Omissions

Mason conceptualizes stress as an interaction between psychological, environmental, and biological variables. The individual’s experience of stress and manifestation of stress responses depends on appraisal of a situation or stimulus, personality factors, situational or environmental influences, and an integrated multihormonal response. He focused on endocrinological responses as evolutionarily functional reactions associated with extreme psychological stress in normal humans and animals. From Bernard and Cannon he took the assumption that biological responses to disruption are homeostatic, prepare the organism for exertion, and are aimed at preserving the organism. Mason adds that psychoendocrine responses are essentially anticipatory in nature (Mason, 1968b).

In general, human studies conducted by Mason and coworkers (Bourne, Rose, & Mason, 1967, 1968; Mason, Giller, Kosten, & Harkness, 1988; Mason, Kosten, Southwick, & Giller, 1990; Poe, Rose, & Mason, 1970; Rose, Poe, & Mason, 1968) demonstrated that the magnitude of corticosteroid responses did not correspond to objective measures of the significance of the threat, particularly in terms of the extent to which it was life-threatening. This suggested that for any individual the significance of any event in the environment could only be interpreted as a function of the interaction of his ego defenses, and the manner in which he perceived the environment. (Bourne et al., 1967, p. 104)

Studies in men under the extreme stressor of combat or threat of combat also revealed the power of psychological forces to influence HPA axis activity. In helicopter ambulance medics corticosteroid levels not only were lower than in a noncombat control group but remained low regardless of whether the individual was in combat (Bourne et al., 1967). The authors attributed stable low corticosteroid levels to the use of complex
psychological defenses that enabled subjects to perceive reality in a way that minimized danger and led to feelings of invincibility and invulnerability. These defenses included feelings of job gratification, prestige accorded by other troops, expressions of gratitude by evacuated casualties, religious beliefs, ritualistic behaviors, and calculations of the probability of being injured or killed.

From these studies and an extensive series of animal studies, Mason and colleagues concluded that (a) responses to psychological stressors were profound, often not linked closely in time with the actual experience, persisted for days or weeks after the stressor ceased, and exhibited marked individual differences; (b) acute hormonal responses are sensitive to subtle differences in the psychological parameters of the stressor (i.e., presence or absence of ambiguity) (Mason, 1968a, 1975, Mason, Mangan, Brady, Conrad, & Rioch, 1961; Mason, Hartley, Mougey, Ricketts, & Jones, 1973); (c) hormonal responses to psychological stress are provoked by anticipated metabolic needs and are aimed at meeting those needs and restoring homeostasis (Mason, 1968a); and (d) the responses of individual hormones during and after stress must be evaluated in a multihormonal context because individual hormones have multiple and sometimes opposing effects on metabolic processes and hormones interact with one another in a complex, mutually regulatory manner at any given time-point as well as over time (Mason, 1968b).

Mason also counters Selye’s nonspecificity concept. He notes that endocrinological responses to physical stressors such as heat, cold, blood loss, and hyperinsulinemia counter the challenge in specific homeostatic ways rather than in nonspecific ways (Mason, 1971, 1975). Second, Mason points out that physical stressors such as fasting, exercise, cold, and heat have inherent psychological stress components. Mason argues that the effects of physical stressors have historically been confounded with effects of psychological stress and demonstrated empirically that when psychological components are reduced or eliminated, adrenocortical responses are also reduced or eliminated (Mason, Jones, Ricketts, Brady, & Tolliver, 1968; Mason, Wool, Mougey, Wherry, Collins, & Taylor, 1968). The major disadvantage of Mason’s psychobiological stress model is the failure to entertain the possibility that psychological and biologic responses may interact in a bidirectional manner. Like Lazarus, Mason’s theoretical approach assumes a top-down process in which psychological factors affect biological processes, but not vice versa.

5. CONCLUSIONS

Theory as a guide for empirical work is essential to making progress in a field. In Lewin’s words, “it is an illusion to believe that is possible to develop on a purely empirical basis any science which deals with questions of interdependence and causation” (Lewin, 1938, p. 12). How stress, health, and illness are defined, therefore, guides the choice of question under investigation, the design of experiments, the interpretation of data, and the choice of future directions. Given the retrospective clarity that historical consideration offers, it is clear that better understanding of the relationship between stress and disease requires viewing the individual as a psychobiological entity. Psychological forces are the perceptible core of human existence: awareness of self, the relevance of the threat or challenge to self, and cognitive and behavioral responses aimed at preserving self. Biological forces operate largely beneath the level of psychological awareness, are
evolutionarily old, and follow their own mute teleology of homeostasis—another form of self-preservation.

The challenge for stress researchers in the 21st century is to discover the mechanisms by which individual differences that are the product of culture, gender, environment, personal history, personality, genotype, physiology, and neurochemistry make the individual vulnerable or resistant to stress-induced physical and psychological disease. Approaches to this challenge that incorporate awareness of humans as psychobiological entities and that comprise a variety of methodological tools are the most likely to make important contributions to the field.

REFERENCES


