CATECHOLAMINES AND STRESS

DAVID S. GOLDSTEIN

Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, e-mail: goldsteind@ninds.nih.gov

The subject of catecholamines and stress has occupied researchers for many years and filled many books. A brief revew such as this cannot cover such a broad topic. Instead, provided here are a few concepts, reflecting somewhat different viewpoints from those in standard textbooks.

The first of these concepts is that there are three distinct peripheral catecholamine systems, each with different effectors, regulation, and roles. The three systems are the sympathetic nervous system, adrenomedullary hormonal system, and DOPA-dopamine autocrine/paracrine system. This contrasts with the traditional concept, promulated by WALTER B. CANNON, of a unitary sympathoadrenal system. It also contrasts with the notion of HANS SELYE that release of "adrenalines" characterizes the acute phase of what he called the "General Adaptation Syndrome."

Both these investigators held to the view that all forms of stress lead to the same stereotyped response. Indeed, in line with this "doctrine of nonspecificity," SELYE defined stress as the *nonspecific* response of the body to any demand imposed upon it [1]. According to a relatively new concept, however, stress responses have a primitive kind of specificity, with differential responses of the sympathetic nervous and adrenomedullary hormonal systems, depending on the type and intensity of the stressor as sensed by the organism and interpreted in light of experience [2].

Another concept in this paper that contrasts with CANNON's teachings is that instead of the sympathetic nervous system becoming active only in emergencies, tonic sympathetic nervous outflows to several vascular beds, organs, and glands maintain levels of a variety of monitored variables, both under resting conditions and in response to everyday challenges such as orthostasis, locomotion, the post-prandial state, and altered temperature.

This paper also notes a closer association between the hypothalamo-pituitary-adrenocortical system and adrenomedullary hormonal system in several forms of stress than between the sympathetic nervous and adrenomedullary hormonal systems (Table 1). In fainting, adrenomedullary activation with concurrent sympathoinhibition precedes and may precipitate the acute neurocirculatory collapse.

Finally, offered for consideration here is the notion that stress and distress can contribute to acute and chronic diseases, by worsening independent pathologic states and inducing "allostatic load."

These concepts may provide a theoretical basis for scientific integrative medicine in the post-genome era.

Three peripheral catecholamine systems

WALTER B. CANNON, extending CLAUDE BERNARD'S concept of the *milieu intérieur,* taught that coordinated body processes work toward the goal of an ideal set of steady-states, for which he coined the term, "homeostasis" [3-5]. CANNON's research was the first to document the role of adrenal secretion in rapid responses of the organism to threats to homeostasis [6,7].

CANNON taught that the adrenal gland and sympathetic nervous system functioned as a unit. Indeed, in 1939, he formally proposed epinephrine (adrenaline) not only as the active principle of the adrenal gland but also as the neurotransmitter of the sympathetic nervous system [8]. If this had proven to be the case, this would have confirmed

Table 1.
Hypothalamo-pituitary-adrenocortical (HPA), adrenomedullary hormonal system (AHS), and sympathetic nervous system (SNS) responses to different stressors

Condition	HPA	AHS	SNS	References
Active Escape/Avoidance in rats	+	+	++	75,79
Cardiac Arrest (or Bypass)	+++	++++	++	99-106
Cold Exposure, Hypothermia	+	++	++++	69-72
Cold Exposure, No Hypothermia	0	+	+++	29,37,64-68
Exercise	+	++	+++	65,82-85
Exercise to Exhaustion	++	+++	++++	84,86,87
Fainting	++	++++	0	44,50,51,89
Glucoprivation	+++	++++	+	29,58,59
Handling in rats	++	++	+	29,92,93
Hemorrhagic Hypotension	+++	+++	+	29,60-63
Hemorrhage, No Hypotension	+	+	++	29,60
Immobilization in rats	++++	++++	++++	29,90-92
Laboratory Mental Challenge	++	++	+	26,80,81
Pain	++	+++	++	5,29,73,74
Passive/Immobile Fear	++	+++	+	5,75-79
Public Performance	++	+++	+	26,85,88
Social Stress in rhesus monkeys	++	++	++	107
Surgery	+	+	++	94-98

Notes: Different intensities are indicated from 0 through ++++, based on the cited References, weighed equally. There is a generally closer association between AHS and HPA than between AHS and SNS responses.

the functional unity of the the sympathoadrenal system. In 1946, however, about a year after CANNON'S death, VON EULER correctly identified norepinephrine as the sympathetic neurotransmitter [9]. As discussed below, the notion of a unitary sympathoadrenal system continues in medical thinking [10-13], despite persuasive evidence for differential changes in sympathetic nervous and adrenomedullary hormonal activities not only with different forms of stress [13] but also as a function of variables such as aging and obesity [14,15].

Dopamine, the third member of the small family of endogenous catecholamines besides norepinephrine and epinephrine, functions in the brain as a neurotransmitter. Understanding of its functions in the periphery has lagged behind. At least in some organs, most notably the kidneys, dopamine seems to function neither as a neurotransmitter, released from putative dopaminergic nerves or co-released with norepinephrine from sympathetic nerves, nor as a hormone, released from the adrenal medulla along with epinephrine. Instead, dopamine production in the kidneys appears to depend mainly on uptake of its precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), from the circulation, with conversion to dopamine by L-aromatic-amino-acid decarboxylase in proximal tubular - i.e., non-neuronal and non-chromaffin - cells [16,17]. Dopamine exiting the cells then appears to act as an autocrine/paracrine substance, promoting natriuresis by local inhibition of Na^{+}/K^{+} ATPase.

More of dopamine production and metabolism take place in the mesenteric organs than in the brain, sympathetic nerves, or adrenal chromaffin cells [18]. At least some of this production arises from tyrosine hydroxylase being expressed in non-neuronal cells such as gastric parietal, pancreatic acinar, and lamina propria cells [19,21]. It is possible that locally produced dopamine contributes to regulation of gastrointestinal motility or bicarbonate secretion.

Tonic activity of the sympathetic nervous system

According to CANNON rapid activation of homeostatic systems - especially of the "sym-

pathaodrenal system" - in emergencies would preserve the internal environment, by producing compensatory and anticipatory adjustments that would enhance the likelihood of survival. In the sheltered confines of a laboratory, however, with controlled temperature and *ad libitum* water, nutrients, and calories, mammals did not seem to require an intact sympathetic nervous system [22].

Compensatory activation of other vasoactive systems after destruction of the sympathetic nervous system helps to explain why many workers, including CANNON, erroneously concluded that the sympathetic nervous system acts only as an "emergency" system [23,24]. By now it is appreciated that even under resting conditions, pulse-synchronous bursts of skeletal muscle sympathetic nerve activity and plasma levels of norepinephrine are readily detectable, and norepinephrine continuously enters the venous drainage of most organs. Moreover, ganglion blockade abolishes skeletal sympathetic nerve traffic and markedly decreases plasma norepinephrine levels; and interference with ganglionic neurotransmission, destruction of sympathetic nerves or blockade of catecholamine receptors consistently decreases blood pressure.

It is also by now clear that activities of daily life, such as meal ingestion [25], public speaking [26], changing posture [27], and movement - i.e., not only emergencies - are associated with continual alterations in sympathetic nervous system outflows, maintaining appropriate blood flow to the brain, body temperature, delivery of metabolic fuel to body organs, and so forth. Each of these activities is associated with a somewhat different set of "normal" apparent steady-states, directed by the brain and determined by coordinated actions of a variety of effector systems. This principle leads directly to the concept of "allostasis," discussed below.

Specificity vs. non-specificity of responses to stressors

According to CANNON, whether the threat were exposure to cold, hemorrhage, hypoglycemia, or distressing emotional encounters, the response in these emergencies would be essentially the same [3,5].

SELYE introduced and popularized stress as a medical scientific idea. According to SELYE'S theory, "Stress is the nonspecific response of the body to any demand upon it [1]. Responses to stressors would have specific and nonspecific components, and he referred to only the nonspecific component as "stress." After removal of specific responses from consideration, a nonspecific syndrome would remain. Although nonspecific with respect to the inciting agents, the stress response itself was viewed to consist of a stereotyped pathological pattern, with enlargement of the adrenal glands, involution of the thymus gland (associated with atrophy of lymph nodes and inhibition of inflammatory responses), and peptic bleeding or ulceration. CHROUSOS and Gold [28] modified the doctrine of nonspecificity, by proposing that above a threshold intensity, any stressor would elicit the "stress syndrome." More than a half century elapsed before SELYE'S doctrine of nonspecificity underwent experimental testing, which failed to confirm it [29].

By now researchers have largely abandoned both CANNON'S and SELYE'S notions of stereotyped, nonspecific neuroendocrine responses regardless of the stressor. More modern theories view stress as a sensed threat to homeostasis [30,31], where the response has a degree of specificity, depending among other things on particular challenge to homeostasis and the organism's perception of the stressor and ability to cope with it [32].

A homeostatic definition of stress

Stress occurs when the organism perceives a disruption or a threat of disruption of homeostasis. Central to the present theory is that the body possesses numerous homeostatic comparators, which have been called "homeostats" [33]. Each homeostat compares information with a setpoint for responding, determined by a regulator. Homeostatic systems typically use multiple effectors to change values for the controlled variable. The loop is closed by monitoring changes in the levels of the controlled variable, via one or more monitored variables.

By analogy, in a home temperature control system, the thermostat plays a central role, by sensing

discrepancy between the setpoint, determined by a regulator, and the temperature, which produces differential bending of metal bands in the thermostat. This type of system is a classical example of regulation by negative feedback. Home temperature control systems always include multiple effectors. The redundancy comes at relatively little cost, compared with three advantages. The multiplicity extends the range of control of external temperatures where the internal temperature can be maintained; when a single effector fails to function, others are activated compensatorily, helping maintain the temperature at about the set level; and one can pattern the use of the effectors as appropriate to maximize economy and efficiency.

A tremendous array of homeostatic systems detect perturbations of monitored variables. In line with the home heating analogy, this even includes afferent information to the brain about cutaneous and blood temperature, leading to altered activities of cholinergic and noradrenergic nerve fibers in the skin that regulate sweating and vasomotor tone [34].

Principles of homeostatic system operation

Homeostatic systems operate according to a few principles, which, despite their simplicity, can explain complex physiological phenomena and help to resolve persistently controversial issues in the area of stress and disease. Homeostatic systems always include regulation by negative feedback. Increases in values of the monitored variable result in changes in effector activity that oppose and thereby "buffer" changes in that variable. This feedback regulation can be modulated at several levels and therefore can be quite complex.

Homeostatic systems generally use more than one effector, for the same reasons as home temperature control systems. Effector redundancy extends the ranges of control of monitored variables. It enables compensatory activation of alternative effectors, assuming no change in homeostat settings. Examples of compensatory activation in physiology include augmentation of sympathoneural responsiveness by adrenalectomy, hypophysectomy, or thyroidectomy [35-37]. Finally, effector redundancy introduces the potential for patterned effector responses. Patterning of neuroendocrine, physiological, and behavioral effectors increases the likelihood of adaptiveness to the particular challenge to homeostasis, providing another basis for natural selection to favor the evolution of systems with multiple effectors.

Different homeostats can regulate the activity of the same effector system. For instance, the osmostat and volustat share the vasopressin effector [38]. Blockade of afferent information to or interference with the function of a homeostat increases the variability of levels of the monitored variable. Thus, baroreceptor deafferentiation increases the variability of blood pressure, as does bilateral destruction of the nucleus of the solitary tract, the likely brainstem site of the arterial barostat [39].

Even a simple homeostatic reflex reflects stress, when a perceived discrepancy between a setpoint for a monitored variable and information about the actual level of that variable elicits compensatory responses to decrease the discrepancy. One way of looking at stress is as a condition where expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match the current or anticipated perceptions of the internal or external environment, and this discrepancy between what is obser-ved or sensed and what is expected or programmed elicits patterned, compensatory responses.

What is distress?

Distress is aversive to the organism, as evidenced by motivation for learning to escape or avoid the stressor. The homeostat theory does not assume an equivalence of noxiousness (i.e., negatively reinforcing properties) with production of pathological changes; that is, the theory does not assume that distress causes disease. In contrast, SELYE characterized distress as unpleasant or harmful [1], without separating these two very different characteristics. He never incorporated the relationship between distress and disease explicitly in his theory. As noted above, SELYE's theory emphasized the nonspecificity of the stress response, whereas according to the homostatic theory, the experience of distress responses depends on the character, intensity, and meaning of the stressor

as perceived by the organism and on the organism's perceived ability to cope with it. Distress responses, as all stress responses, have a "purpose," mitigating effects of a stressor in some way. This applies not only to neuroendocrine aspects of those responses (such as the glucose counterregulatory actions of pituitary-adrenocortical and adrenomedullary stimulation during insulin-induced hypoglycemia) but also to psychological aspects (such as conditioned aversive and instrumental avoidance learning). Distress responses evolved and probably continue to be expressed even in higher organisms, including humans who actually are only rarely exposed to truly "fight-or-flight" agonistic encounters, because of the importance of those responses in instinctive communication. SELYE'S theory did not consider the communication aspect of distress.

Allostasis and allostatic load

Levels of physiological activity required to reestablish or maintain homeostasis differ, depending on continually changing conditions in which the organism finds itself - e.g., running vs standing vs lying down. "Allostasis," a term used by STERLING and EYER in 1988 [40], refers to levels of activity required for the individual to "maintain stability through change" - i.e., to adapt [40-42]. In terms of the homeostatic theory, "allostasis" refers to the set of apparent steady-states maintained by multiple effectors. In the analogy of the home temperature control system, one can regulate temperature at different levels, by appropriate use of effectors. Among individuals, levels of glucose, blood pressure, body temperature, metabolism, and so forth can be held stable at different levels, with different patterns of effector activation.

Homeostat resetting redefines the conditions required to maintain homeostasis. Regulation around an altered apparent steady-state is the essence of allostasis. This would be analogous to a different thermostatic setting in the winter compared to the summer. A neuroendocrine example would be the hyperglycemia of exercise. Even in anticipation of the need for metabolic fuel, by activation of "central command," the blood glucose level increases to a new steady-state value. Resetting alters activities of multiple effector systems required to maintain allostasis, at least for short durations. During stress, short-term changes in homeostatic settings generally enhance the long-term well-being and survival of the organism. Responses during exercise provide an obvious example. When superimposed on a substrate of pathology, however, homeostatic resetting can cause harm. For instance, in the setting of ischemic heart disease, global or patterned increases in sympathetic outflows from homeostat resetting would increase cardiac work, the resulting imbalance between oxygen supply and demand precipitating angina pectoris, myocardial infarction, or sudden death.

"Allostatic load" [43] refers to effects of prolonged continuous or intermittent activation of effectors involved in allostasis. In the analogy of the home temperature control system, allostatic load would increase if a window or door were left open. In this situation, one or more effectors might be activated frequently or even continuously. An even more extreme example would be having the air conditioner and the furnace on at the same time, as is the case in an overheated apartment in the spring when there is a warm day before the boilers have been shut down. Continued use of the furnace and air conditioner in opposition to one another, an example of an inefficient "allostatic state," consumes fuel and contributes to wear-and-tear on both pieces of equipment. Long-term allostatic load - the wear and tear cost of adaptation -provides a conceptual basis for studying long-term health consequences of stress.

Stressor-specific responses of catecholamine systems

After adequately sensitive assay methods for plasma levels of norepinephrine and epinephrine became available, evidence rapidly accumulated for different noradrenergic vs. adrenergic responses in different situations [10,44-46]. A new concept began to emerge, in which norepinephrine levels, and thereby overall sympathetic nervous "activity", would play key roles in appropriate distribution of blood volume and homeostasis of

blood pressure (or blood delivery to the brain), such as during orthostasis, cold exposure, mild blood loss, locomotion, exercise, altered salt intake, and water immersion. Epinephrine levels, and thereby adrenomedullary hormonal system "activity," would respond to global or metabolic threats, such as hypoglycemia, hemorrhagic hypotension, exercise beyond an anerobic threshold, asphyxiation, emotional distress, and shock. Evidence also has accumulated for an association between norepinephrine and active escape, avoidance, or attack, and an association between epinephrine and passive, immobile fear. Table 1 provides some examples of different patterns of sympathetic nervous, adrenomedullary hormonal, and hypothalamo-pituitary-adrenocortical responses to different stressors.

Thus, in contrast with the doctrine of nonspecificity, according to the homeostatic theory of stress, activities of effector systems are coordinated in relatively specific patterns, including neuroendocrine patterns. These patterns serve different needs, and the sympathetic nervous and adrenomedullary hormonal systems play important roles in many of them. For instance, sympathetic nervous system activation predominates in response to orthostasis, moderate exercise, and exposure to cold, whereas adrenomedullary hormonal system activation predominates in response to glucoprivation and emotional distress (Table 1).

In terms of the body's thermostat, studies of humans exposed to cold or with mild core hypothermia have provided support for the notion of primitive specificity of neuroendocrine stress responses. Cold exposure increases plasma norepinephrine levels, with smaller increases in plasma epinephrine levels, consistent with sympathetic neuronal activation and relatively less adrenomedullary hormonal activation. Mild core hypothermia also increases antecubital venous levels of norepinephrine but not epinephrine [34]. Both norepinephrine and epinephrine levels in arterial plasma increase in this setting, but with larger norepinephrine responses. These findings make sense, in that one can maintain body temperature effectively by sympathetically-mediated cutaneous vasoconstriction, piloerection, and shivering. When these mechanisms give way, and core temperature falls, then high circulating epinephrine levels increase generation of calories [47], associated with the experience of distress, which motivates escape and avoidance, and augments norepinephrine release from sympathetic nerve terminals for a given amount of nerve traffic [48].

For each stress, neuroendocrine and physiological changes are coupled with behavioral changes. For instance, the regulation of total body water in humans depends on an interplay between behavior (the search for water and drinking), an internal experience or feeling (thirst), and the elicitation of a neurohumoral response pattern (in this case dominated by vasopressin, the antidiuretic hormone; and to a lesser extent angiotensin, a potent stimulator of drinking). Evoked changes in homeostat function often produce not only neuroendocrine and physiological effects but also behavioral responses; however, because of traditional boundaries among physiology, endocrinology, and psychology, interactions producing integrated patterns of response remain incompletely understood.

Medical and psychological consequences of stress and allostasis

Induction of a positive feedback loop in a homeostatic system evokes instability. An example would be renin-angiotensin-aldosterone system activation in congestive heart failure. Activation of this system increases sodium retention and vascular tone, leading to increased cardiac preload and afterload that worsen the congestive heart failure. Therefore, treatment with an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker can successfully treat congestive heart failure [49].

Another example may be fainting reactions. Fainting is preceded by high circulating epinephrine levels and withdrawal of sympathetic vasoconstrictor tone [50,51]. This elicits skeletal muscle vasodilation, and total peripheral resistance to blood flow falls. If there were enough "shunting" of blood to the skeletal muscle, then blood flow to the brainstem might fall. The person would not feel "right." This could evoke more adrenomedullary secretion of epinephrine, and the consequent neurocircula-

tory positive feedback loop would lead to critical brainstem hypoperfusion and loss of consciousness within seconds to minutes.

In people who faint repeatedly, it is often the case that between episodes they do not feel normal. Patients who are susceptible to neurocardiogenic syncope often complain of chronic fatigue, headache, chest pain, orthostatic intolerance, difficulty concentrating, and heat intolerance, which can be debilitating. The patients also have tonic suppression of norepinephrine spillover from the heart [52]. In essence this may reflect consequences of long-term allostatic load, as discussed below.

Induction of a positive feedback loop "nested" in a larger system that includes negative feedback can lead to a new steady-state group of settings and values for monitored variables, rather than "explosion" of the system. For example, a distressing situation might elicit fear, resulting in release of norepinephrine in the brain and epinephrine in the periphery, both of which could augment vigilance behavior and heighten the experience of distress, resulting in greater fear [53]. The organism could enter an "escape mode," with a different set of homeostatic regulatory settings; however, there is a risk of the positive feedback loop leading to a behavioral "explosion", panic, or a pathophysiologic "explosion", pulmonary edema. The notion of induction of a nested positive feedback loop can also provide a model for developmental changes in adolescence, where stability would actually be abnormal, but there is a greater chance for both psychological and physiological disorders to emerge.

The homeostatic theory of stress and the concept of allostasis can help understand chronic as well as acute medical consequences of stress. Chronic activation of allostatic effectors in allostatic states increases allostatic load. For instance, chronic elevations in adrenomedullary and hypothalamic-pituitary-adrenocortical outflows may worsen insulin resistance, and chronic cardiac sympathetic activation may accelerate cardiovascular hypertrophy and development of heart failure [54].

Another application of the homeostatic idea to medical consequences of stress is in terms of the perceived ability to cope. As noted above, an organism experiences distress upon sensing that the effector responses will not be sufficient to restore or maintain allostasis. In contrast with distress, stress does not imply a conscious experience. For instance, even heavily sedated humans have substantial adrenomedullary stimulation in response to acute glucoprivation. Indeed, the larger adrenomedullary response to the same stressor in alert than in sedated humans might provide a measure of the distress. Distress instinctively elicits observable signs and pituitary-adrenocortical and adrenomedullary activation [2,32]. Via these neuroendocrine changes, distress could worsen pathophysiologic processes. For instance, because of adrenomedullary activation, in a patient with coronary artery stenosis, distress could elicit cardiovascular stimulation and produce an excess of myocardial oxygen consumption over supply, precipitating myocardial infarction or lethal ventricular arrhythmias. Moreover, long-term distress could augment both the risk of a mood disorder and the risk of worsening coronary disease.

Long-term physical or mental consequences of stress would depend on long-term effects of allostatic load. Prolonged, intensive activation of effector systems could exaggerate effects of intrinsic defects in any of them, just as increased air pressure in a tire could expand and eventually "blow out" a weakened area. It is not difficult to imagine that repeated or long-term stress or distress could lead to a medical or psychiatric "blow-out."

Maintenance of allostatic states requires energy. This requirement is perhaps clearest in allostasis of core temperature. In mammals, maintenance of a constant core temperature accounts for a substantial proportion of total body energy expenditure at rest. One may hypothesize that reducing allostatic load exerts beneficial health effects, just as one may hypothesize that excessive allostatic load exerts deleterious health effects. In the analogy of the home temperature control system, maintaining a temperature of 60 degrees Fahrenheit in the summer would require a great expenditure of energy and involve cooling systems being on continuously, whereas in the winter, maintaining the same temperature

would be energy-efficient. One can imagine that the likelihood of system breakdown would depend on the extent of long-term energy use by the effector systems.

Chronic effector system activation might alter the efficiency of the homeostatic system itself. For instance, chronic sympathetic nervous stimulation of the cardiovascular system could promote cardiovascular hypertrophy, "splinting" arterial baroreceptors in stiff blood vessel walls, in turn contributing to systolic hypertension and the risk of heart failure, kidney failure, and stroke.

Moreover, an inappropriately large adrenomedullary response to a stressor might exaggerate the experience of emotional distress [55]. Exaggerated distress responses might increase the risk of worsening an independent pathologic process, such as in panic-induced angina pectoris [56,57].

In summary, this essay reflects a merging of the homeostat theory of stress with the concept of allostatic load, in attempting to understand the relationships among stress, catecholamines, and disease. Until this conceptual merging, the homeostat theory did not lead easily to testable predictions about long-term effects of stress and distress; and the concept of allostatic load did not incorporate determinants of that load as sensed discrepancies between afferent information and setpoints for responding, leading to patterned alterations in activities of multiple effectors. Merging of the homeostat theory of stress with the notions of allostasis and allostatic load can provide a basis for explaining and predicting physical and psychiatric effects of acute and chronic stress.

Stress is an interdisciplinary topic, and understanding health consequences of stress requires an integrative approach. Research and ideas about stress must must move beyond considering only one effector system, such as the "sympathoadrenal system," and only one monitored variable, such as serum glucose levels, to incorporate multiple effectors and multiple homeostatic systems that are regulated in parallel. They must also move beyond the notion of a single set of ideal values for monitored variables – homeostasis – to incorporate dynamic changes in homeostatic settings - allostasis. Merging of the homeostatis definitions of stress and distress with the concept of allostasis should provide a better understanding of the roles of stress and distress, via catecholamine systems, in chronic diseases and also provide a conceptual basis for the further development of scientific integrative medicine.

References

1. Selye H: Stress without Distress. New York: New American Library; 1974.
2. Goldstein DS: Stress, Catecholamines, and Cardiovascular Disease. New York: Oxford University Press; 1995.
3. Cannon WB: The Wisdom of the Body. New York: W.W. Norton; 1939.
4. Cannon WB: Organization for physiological homeostasis. Physiol Rev 1929; **9**: 399-431, 1929
5. Cannon WB: Bodily Changes in Pain, Hunger, Fear and Rage. New York: D. Appleton & Co.; 1929.
6. Cannon WB, de la Paz D: Emotional stimulation of adrenal gland secretion. Am J Physiol **28:** 64-70, 1911
7. Cannon WB: The emergency function of the adrenal medulla in pain and in the major emotions. Am J Physiol **33:** 356-372, 1914
8. Cannon WB, Lissak K:. Evidence for adrenaline in adrenergic neurones. Am J Physiol **125:** 765-777, 1939
9. von Euler US: A specific sympathomimetic ergone in adrenergic nerve fibres (sympathin) and its relations to adrenaline and nor-adrenaline. Acta Physiol Scand **12:** 73-96, 1946
10. Cryer PE. Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. N Engl J Med **303:** 436-444, 1980
11. Shah SD, Tse TF, Clutter WE, Cryer PE: The human sympathochromaffin system. Am J Physiol **247:** E380-E384, 1984
12. Sofuoglu M, Nelson D, Babb DA, Hatsukami DK: Intravenous cocaine increases plasma epinephrine and norepinephrine in humans. Pharmacol Biochem Behav **68:** 455-459, 2001

13. KVETNANSKY R, PACAK K, FUKUHARA K, VISKUPIC E, HIREMAGALUR B, NANKOVA B, GOLDSTEIN, DS, SABBAN EL, KOPIN IJ: Sympathoadrenal system in stress. Interaction with the hypothalamic-pituitary-adrenocortical system. Ann NY Acad Sci **771:** 131-158, 1975
14. SEALS DR, ESLER MD. Human ageing and the sympathoadrenal system. J Physiol **528:** 407-417, 2000
15. DEL RIO G. Adrenomedullary function and its regulation in obesity. Int J Obes Relat Metab Disord **24 Suppl 2:** S89-S91, 2000
16. BROWN MJ, DOLLERY CT: A specific radioenzymatic assay for dihydroxyphenylalanine (DOPA). Plasma dopa may be the precursor of urine free dopamine. Br J Clin Pharmacol 11: 79-83, 1981
17. WOLFOVITZ E, GROSSMAN E, FOLIO CJ, KEISER HR, KOPIN IJ, GOLDSTEIN DS: Derivation of urinary dopamine from plasma dihydroxyphenylalanine in humans. Clin Sci (Colch) **84:** 549-557, 1993
18. EISENHOFER G, ANEMAN A, FRIBERG P, KEISER HR, KOPIN IJ, GOLDSTEIN DS: Substantial production of dopamine in the human gastrointestinal tract. J Clin Endocrinol Metab **42:**374-377, 1998
19. MEZEY E, EISENHOFER G, HANSSON S , HUNYADY B, HOFFMAN BJ: Dopamine produced by the stomach may act as a paracrine/autocrine hormone in the rat. Neuroendocrinology **67:** 336-348, 1998
20. MEZEY E, EISENHOFER G, HARTA G HANSSON S, GOULD L, HUNYADY B, HOFFMAN BJ: A novel nonneuronal catecholaminergic system: Exocrine pancreas synthesizes and releases dopamine. Proc Natl Acad Sci **93:** 10377-10382, 1996
21. MEZEY E, EISENHOFER G, HANSSON S, HARTA G, HOFFMAN BJ, GALLATZ K, PALKOVITS M, HUNYADY B. Non-neuronal dopamine in the gastrointestinal system. Clin Exp Pharmacol Physiol **26:** S14-S22, 1999
22. CANNON WB. The effects of progressive sympathectomy on blood pressure. Am J Physiol **97:** 592-595, 1931
23. GAUTHIER P, NADEAU R, DE CHAMPLAIN J. Acute and chronic cardiovascular effects of 6-hydroxydopamine in dogs. Circ Res **31:** 207-217, 1972
24. JULIEN C, KANDZA P, BARRES C, LO M, CERUTTI C, SASSARD J. Effects of sympathectomy on blood pressure and its variability in conscious rats. Am J Physiol **259:** H1337-H1342, 1990
25. PATEL JN, COPPACK SW, GOLDSTEIN DS, MILES JM, EISENHOFER G. Norepinephrine spillover from human adipose tissue before and after a 72-hour fast. J Clin Endocrinol Metab **87:** 3373-3377, 2002
26. GERRA G, ZAIMOVIC A, MASCETTI GG, GARDINI S, ZAMBELLI U, TIMPANO M, RAGGI MA, BRAMBILLA F. Neuroendocrine responses to experimentally-induced psychological stress in healthy humans. Psychoneuroendocrinology **26:** 91-107, 2001
27. LAKE CR, ZIEGLER MG, KOPIN IJ. Use of plasma norepinephrine for evaluation of sympathetic neuronal function in man. Life Sci **18:** 315-1325, 1976
28. CHROUSOS GP, GOLD PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. J Am Med Assoc **267:** 1244-1252, 1992
29. PACAK K, PALKOVITS M, YADID G, KVETNANSKY R, KOPIN IJ, GOLDSTEIN DS. Heterogeneous neurochemical responses to different stressors: A test of Selye's doctrine of nonspecificity. Am J Physiol **275:** R1247-R1255, 1998
30. MCEWEN B, STELLAR E. Stress and the individual. Mechanisms leading to disease. Arch Int Med **153:** 2093-2101, 1993
31. GOLDSTEIN DS, MCEWEN B. Allostasis, homeostats, and the nature of stress. Stress. **5:** 55-58, 2002
32. GOLDSTEIN DS. The Autonomic Nervous System in Health and Disease. New York, NY: Marcel Dekker, New York 2001
33. GOLDSTEIN DS. Stress as a scientific idea: A homeostatic theory of stress and distress. Homeostasis **4:** 177-215, 1995
34. FRANK SM, HIGGINS MS, FLEISHER LA, SITZMANN JV, RAFF H, BRESLOW MJ. Adrenergic, respiratory, and cardiovascular effects of core cooling in humans. Am J Physiol **272:** R557-R562, 1997
35. UDELSMAN R, GOLDSTEIN DS, LORIAUX DL, CHROUSOS GP. Catecholamine-glucocorticoid interactions during surgical stress. J Surg Res **43:** 539-545, 1987
36. GOLDSTEIN DS, GARTY M, BAGDY G, SZEMEREDI K, STERNBERG EM, LISTWAK S, DEKA-STAROSTA A, HOFFMAN A, CHANG PC, STULL R, GOLD PW, KOPIN IJ. Role of CRH in glucopenia-induced adrenomedullary activation in rats. J Neuroendocrinol **5:** 475-486, 1993.
37. FUKUHARA K, KVETNANSKY R, CIZZA G, PACAK K, OHARA H, GOLDSTEIN DS, KOPIN IJ: Interrelations between sympathoadrenal system and hypothalamo-pituitary-adrenocortical/thyroid systems in rats exposed to cold stress. J Neuroendocrinol **8:** 533-541, 1996
38. QUILLEN EW, JR., COWLEY AW, JR. Influence of volume changes on osmolality-vasopressin relationships in conscious dogs. Am J Physiol **244:** H73-H79, 1983
39. NATHAN MA, REIS DJ. Chronic labile hypertension produced by lesions of the nucleus
tractus solitarii in the cat. Circ Res **40:** 72-81, 1977
40. MCEWEN BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann NY Acad Sci. **840:** 33-44, 1998

41. SCHULKIN J, GOLD PW, MCEWEN BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. Psychoneuroendocrinology **23:** 219-243, 1998
42. MCEWEN BS. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology **22:** 108-124, 2000
43. MCEWEN BS, STELLAR E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med **153:** 2093-2101, 1993
44. ROBERTSON DA, JOHNSON GA, ROBERTSON RM, NIES AS, SHAND DG, OATES JA. Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. Circulation **59:** 637-643, 1979
45. YOUNG JB, LANDSBERG L. Sympathoadrenal activity in fasting pregnant rats: Dissociation of adrenal medullary and sympathetic nervous system responses. J Clin Invest **64:** 109-116, 1979
46. YOUNG JB, ROSA RM, LANDSBERG L. Dissociation of sympathetic nervous system and adrenal medullary responses. AmJ Physiol **247:** E35-E40, 1984
47. STATEN MA, MATTHEWS DE, CRYER PE, BIER DM. Physiological increments in epinephrine stimulate metabolic rate in humans. Am J Physiol **253:** E322-E330, 1987
48. CHANG PC, GROSSMAN E, KOPIN IJ, GOLDSTEIN DS. On the existence of functional beta-adrenoceptors on vascular sympathetic nerve endings in the human forearm. J Hypertens **12:** 681-690, 1994
49. KLUGER J, CODY RJ, LARAGH JH. The contributions of sympathetic tone and the renin-angiotensin system to severe chronic congestive heart failure: response to specific inhibitors (prazosin and captopril). Am J Cardiol **49:** 1667-1674, 1982
50. MOSQUEDA-GARCIA R, FURLAN R, FERNANDEZ-VIOLANTE R, DESAI T, SNELL M, JARAI Z, ANANTHRAM V, ROBERTSON RM, ROBERTSON D. Sympathetic and baroreceptor reflex function in neurally mediated syncope evoked by tilt. J Clin Invest **99:** 2736-2744, 1997
51. GOLDSTEIN DS, HOLMES C, FRANK SM, NAQIBUDDIN M, DENDI R, SNADER S, CALKINS H. Sympathoadrenal imbalance before neurocardiogenic syncope. *Am. J. Cardiol.* 2003; 91:53-58.
52. GOLDSTEIN DS, HOLMES C, FRANK SM, DENDI R, CANNON RO, 3RD, SHARABI Y, ESLER MD, EISENHOFER G. Cardiac sympathetic dysautonomia in chronic orthostatic intolerance syndromes. *Circulation*. 2002; 106:2358-65.
53. ASTON-JONES G, RAJKOWSKI J, KUBIAK P, ALEXINSKY T. Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *J Neurosci.* 1994; 14:4467-4480.
54. RUNDQVIST B, ELAM M, BERGMANN-SVERRISDOTTIR Y, EISENHOFER G, FRIBERG P. Increased cardiac adrenergic drive precedes generalized sympathetic activation in human heart failure. *Circulation.* 1997; 95:169-175.
55. SCHACHTER S, SINGER J. Cognitive, social, and physiological determinants of emotional state. *Psychol Rev*. 1962; 69:379-399.
56. WILKINSON DJC, THOMPSON JM, LAMBERT GW, JENNINGS GL, SCHWARZ RG, JEFFREYS D, TURNER AG, ESLER MD. Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. *Arch Gen Psychiatry*. 1998; 55:511-520.
57. MANSOUR VM, WILKINSON DJ, JENNINGS GL, SCHWARZ RG, THOMPSON JM, ESLER MD. Panic disorder: coronary spasm as a basis for cardiac risk? *Med J Australia*. 1998; 168:390-392.
58. WATABE T, TANAKA K, KUMAGAE M, ITOH S, TAKEDA F, MORIO K, HASEGAWA M, HORIUCHI T, MIYABE S, SHIMIZU N. Hormonal responses to insulin-induced hypoglycemia in man. *J Clin Endocrinol Metab*. 1987; 65:1187-91.
59. TOSO CF, RODRIGUEZ RR, RENAULD AR, MARQUEZ AG, LINARES LM. Adrenocorticotrophic hormone, cortisol and catecholamine concentrations during insulin hypoglycaemia in dogs anaesthetized with thiopentone. *Can J Anaesth*. 1993; 40:1084-91.
60. SCHADT JC, LUDBROOK J. Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. *Am. J. Physiol.* 1991; 260:H305-H318.
61. BEREITER DA, ZAID AM, GANN DS. Effect of rate of hemorrhage on sympathoadrenal catecholamine release in cats. *Am J Physiol*. 1986; 250:E69-75.
62. DARLINGTON DN, SHINSAKO J, DALLMAN MF. Responses of ACTH, epinephrine, norepinephrine, and cardiovascular system to hemorrhage. *Am J Physiol*. 1986; 251:H612-8.
63. GRASSLER J, JEZOVA D, KVETNANSKY R, SCHEUCH DW. Hormonal responses to hemorrhage and their relationship to individual hemorrhagic shock susceptibility. *Endocrinol Exp*. 1990; 24:105-16.
64. FRANK SM, HIGGINS MS, BRESLOW MJ, FLEISHER LA, GORMAN RB, SITZMANN JV, RAFF H, BEATTIE C. The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. A randomized clinical trial. *Anesthesiology*. 1995; 82:83-93.

65. Graham TE, Sathasivam P, MacNaughton KW. Influence of cold, exercise, and caffeine on catecholamines and metabolism in men. *J.Appl.Physiol.* 1991; 70:2052-2058.
66. Marino F, Sockler JM, Fry JM. Thermoregulatory, metabolic and sympathoadrenal responses to repeated brief exposure to cold. *Scand.J.Clin.Lab.Invest.* 1998; 58:537-545.
67. Wittert GA, Or HK, Livesey JH, Richards AM, Donald RA, Espiner EA. Vasopressin, corticotrophin-releasing factor, and pituitary adrenal responses to acute cold stress in normal humans. *J. Clin. Endocrinol. Metab.* 1992; 75:750-755.
68. Marino F, Sockler JM, Fry JM. Thermoregulatory, metabolic and sympathoadrenal responses to repeated brief exposure to cold. *Scand J Clin Lab Invest*. 1998; 58:537-45.
69. Gibbs DM. Inhibition of corticotropin release during hypothermia: the role of corticotropin-releasing factor, vasopressin, and oxytocin. *Endocrinology*. 1985; 116:723-7.
70. Frank SM, Cattaneo CG, Wieneke-Brady MB, El-Rahmany H, Gupta N, Lima JA, Goldstein DS. Threshold for adrenomedullary activation and increased cardiac work during mild core hypothermia. *Clin. Sci.* 2002; 102:119-125.
71. Hirvonen J, Huttunen P. Increased urinary concentration of catecholamines in hypothermia deaths. *J Forensic Sci*. 1982; 27:264-71.
72. Chi OZ, Choi YK, Lee DI, Kim YS, Lee I. Intraoperative mild hypothermia does not increase the plasma concentration of stress hormones during neurosurgery. *Can J Anaesth*. 2001; 48:815-8.
73. Harden RN, Duc TA, Williams TR, Coley D, Cate JC, Gracely RH. Norepinephrine and epinephrine levels in affected versus unaffected limbs in sympathetically maintained pain. *Clinical Journal of Pain*. 1994; 10:324-330.
74. Brand HS, Gortzak RA, Palmer-Bouva CC, Abraham RE, Abraham-Inpijn L. Cardiovascular and neuroendocrine responses during acute stress induced by different types of dental treatment. *Int Dent J*. 1995; 45:45-8.
75. de Boer SF, Slangen JL, Van der Gugten J. Plasma catecholamine and corticosterone levels during active and passive shock-prod avoidance behavior in rats: effects of chlordiazepoxide. *Physiol. Behav.* 1990; 47:1089-1098.
76. Nijsen MJ, Croiset G, Diamant M, Stam R, Kamphuis PJ, Bruijnzeel A, de Wied D, Wiegant VM. Endogenous corticotropin-releasing hormone inhibits conditioned-fear-induced vagal activation in the rat. *Eur J Pharmacol*. 2000; 389:89-98.
77. Pitman DL, Natelson BH, Ottenweller JE, McCarty R, Pritzel T, Tapp WN. Effects of exposure to stressors of varying predictability on adrenal function in rats. *Behav Neurosci*. 1995; 109:767-76.
78. Pitman DL, Natelson BH, Ottenweller JE. Classical aversive conditioning of catecholamine and corticosterone responses. *Integr Physiol Behav Sci*. 1992; 27:13-22.
79. Korte SM, Bouws GA, Koolhaas JM, Bohus B. Neuroendocrine and behavioral responses during conditioned active and passive behavior in the defensive burying/probe avoidance paradigm: effects of ipsapirone. *Physiol Behav*. 1992; 52:355-61.
80. Costa A, Martignoni E, Blandini F, Petraglia F, Genazzani AR, Nappi G. Effects of etoperidone on sympathetic and pituitary-adrenal responses to diverse stressors in humans. *Clin Neuropharmacol*. 1993; 16:127-38.
81. Yoshiuchi K, Nomura S, Ando K, Ohtake T, Shimosawa T, Kumano H, Kuboki T, Suematsu H, Fujita T. Hemodynamic and endocrine responsiveness to mental arithmetic task and mirror drawing test in patients with essential hypertension. *Am J Hypertens*. 1997; 10:243-9.
82. Deuster PA, Chrousos GP, Luger A, DeBolt JE, Bernier LL, Trostmann UH, Kyle SB, Montgomery LC, Loriaux DL. Hormonal and metabolic responses of untrained, moderately trained, and highly trained men to three exercise intensities. *Metabolism*. 1989; 38:141-8.
83. Nagata S, Takeda F, Kurosawa M, Mima K, Hiraga A, Kai M, Taya K. Plasma adrenocorticotropin, cortisol and catecholamines response to various exercises. *Equine Vet J Suppl*. 1999; 30:570-4.
84. Schwarz L, Kindermann W. Beta-endorphin, adrenocorticotropic hormone, cortisol and catecholamines during aerobic and anaerobic exercise. *Eur J Appl Physiol Occup Physiol*. 1990; 61:165-71.
85. Dimsdale JE, Moss J. Plasma catecholamines in stress and exercise. *JAMA*. 1980; 243:340-342.
86. Oleshansky MA, Zoltick JM, Herman RH, Mougey EH, Meyerhoff JL. The influence of fitness on neuroendocrine responses to exhaustive treadmill exercise. *Eur J Appl Physiol Occup Physiol*. 1990; 59:405-10.
87. Casa DJ, Maresh CM, Armstrong LE, Kavouras SA, Herrera-Soto JA, Hacker Jr FT, Scheett TP, Stoppani J. Intravenous versus oral rehydration during a brief period: stress hormone responses to subsequent exhaustive exercise in the heat. *Int J Sport Nutr Exerc Metab*. 2000; 10:361-74.
88. Malarkey WB, Lipkus IM, Cacioppo JT. The dissociation of catecholamine and hypothalamic-pituitary-adrenal responses to daily stressors using dexamethasone. *J Clin Endocrinol Metab*. 1995; 80:2458-63.

89. Jardine DL, Melton IC, Crozier IG, Bennett SI, Donald RA, Ikram H. Neurohormonal response to head-up tilt and its role in vasovagal syncope. *Am J Cardiol*. 1997; 79:1302-6.
90. Jezova D, Ochedalski T, Glickman M, Kiss A, Aguilera G. Central corticotropin-releasing hormone receptors modulate hypothalamic-pituitary-adrenocortical and sympathoadrenal activity during stress. *Neuroscience*. 1999; 94:797-802.
91. Tjurmina OA, Armando I, Saavedra JM, Goldstein DS, Murphy DL. Exaggerated adrenomedullary response to immobilization in mice with targeted disruption of the serotonin transporter gene. *Endocrinology*. 2002; 143:4520-6.
92. Kvetnansky R, Goldstein DS, Weise VK, Holmes C, Szemeredi K, Bagdy G, Kopin IJ. Effects of handling or immobilization on plasma levels of 3,4-dihydroxyphenylalanine, catecholamines, and metabolites in rats. *Journal of Neurochemistry*. 1992; 58:2296-2302.
93. Dobrakovova M, Kvetnansky R, Oprsalova Z, Jezova D. Specificity of the effect of repeated handling on sympathetic-adrenomedullary and pituitary-adrenocortical activity in rats. *Psychoneuroendocrinology*. 1993; 18:163-74.
94. Donald RA, Perry EG, Wittert GA, Chapman M, Livesey JH, Ellis MJ, Evans MJ, Yandle T, Espiner EA. The plasma ACTH, AVP, CRH and catecholamine responses to conventional and laparoscopic cholecystectomy. *Clin Endocrinol (Oxf)*. 1993; 38:609-15.
95. Kudoh A, Ishihara H, Matsuki A. Response to surgical stress in elderly patients and Alzheimer's disease. *Can J Anaesth*. 1999; 46:247-52.
96. Friedrich M, Rixecker D, Friedrich G. Evaluation of stress-related hormones after surgery. *Clin Exp Obstet Gynecol*. 1999; 26:71-5.
97. Nguyen NT, Goldman CD, Ho HS, Gosselin RC, Singh A, Wolfe BM. Systemic stress response after laparoscopic and open gastric bypass. *J Am Coll Surg*. 2002; 194:557-66; discussion 566-7.
98. Udelsman R, Norton JA, Jelenich SE, Goldstein DS, Linehan WM, Loriaux DL, Chrousos GP. Responses of the hypothalamic-pituitary-adrenal and renin-angiotensin axes and the sympathetic system during controlled surgical and anesthetic stress. *J. Clin. Endocrinol. Metab.* 1987; 64:986-994.
99. O'Leary MJ, Timmins AC, Appleby JN, Medbak S, Grossman AB, Nathan AW, Hinds CJ. Dissociation of pituitary-adrenal and catecholamine activation after induced cardiac arrest and defibrillation. *Br. J. Anaesth.* 1999; 82:271-273.
100. Little RA, Frayn KN, Randall PE, Yates DW. Plasma catecholamines and cardiac arrest. *Lancet*. 1985; ii:509-510.
101. Foley PJ, Tacker WA, Wortsman J, Frank S, Cryer PE. Plasma catecholamine and serum cortisol responses to experimental cardiac arrest in dogs. *Am. J. Physiol.* 1987; 253:E283-E289.
102. Wortsman J, Frank S, Cryer PE. Adrenomedullary response to maximal stress in humans. *Am.J.Med.* 1984; 77:779-784.
103. O'Leary MJ, Timmins AC, Appleby JN, Medbak S, Grossman AB, Nathan AW, Hinds CJ. Dissociation of pituitary-adrenal and catecholamine activation after induced cardiac arrest and defibrillation. *Br J Anaesth*. 1999; 82:271-3.
104. Lindner KH, Haak T, Keller A, Bothner U, Lurie KG. Release of endogenous vasopressors during and after cardiopulmonary resuscitation. *Heart*. 1996; 75:145-50.
105. Schultz CH, Rivers EP, Feldkamp CS, Goad EG, Smithline HA, Martin GB, Fath JJ, Wortsman J, Nowak RM. A characterization of hypothalamic-pituitary-adrenal axis function during and after human cardiac arrest. *Crit Care Med*. 1993; 21:1339-47.
106. Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology*. 1992; 77:662-8.
107. Habib KE, Weld KP, Rice KC, Pushkas J, Champoux M, Listwak S, Webster EL, Atkinson AJ, Schulkin J, Contoreggi C, Chrousos GP, McCann SM, Suomi SJ, Higley JD, Gold PW. Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. *Proc Natl Acad Sci U S A*. 2000; 97:6079-84.

Corresponding author: David S. Goldstein, M.D.
NINDS, NIH
Building 10 Room 6N252
10 Center Drive, MSC-1620
Bethesda, Maryland 20892-1620
Phone: (301) 496-2103
Fax: (301) 402-0180
E-mail: goldsteind@ninds.nih.gov