The stress response and critical illness: A review

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Objectives: **To describe different paradigms that define the stress response, and to postulate how stress is implicated in the pathophysiology of critical illness.**

Design: **Articles were identified through a search of PubMed and Google Scholar.**

Results: **The stress response represents a bundle of adaptive behavioral, physiological, and cellular responses. Although generally beneficial, an important adverse consequence of excessive stress is organ dysfunction. Many interventions currently applied to the critically ill patient are additive and may contribute to organ dysfunction, renewed deterioration, and impaired or delayed recovery. Resilience (ρ) summarizes the interaction among predisposition factors, injury (or stressors), and the body's allostatic responses. Resilience changes over the course of critical illness but is potentially measurable and may be used to identify at-risk patients and to tailor therapy.**

Conclusion: **Critical illness may represent a stress-related decompensation syndrome mediated by neural, endocrine, bioenergetic, and immune systems. As patients pass through the separate phases of critical illness, consideration should be given to different therapeutic end points. This may be particularly pertinent during the established organ dysfunction phase where targeting of normal values may have deleterious consequences. Improved strategies could thus emerge from an increased knowledge and monitoring of the stress response, and what constitutes an optimal adaptive state as it evolves in the course of critical illness. (Crit Care Med 2012; 40:0–0)**

Key Words: allostasis; critical illness; homeostasis; mitochondria; resilience; stress; stress response

The stress response is a biological system developed over millions of years. Found in both invertebrates and vertebrates, its mere existence in such a variety of biological forms is proof of its success in adapting these organisms to internal or external changes.

Stress is a regular accompaniment and an important part of normal daily living. It tones the body, sharpens the mind, and enables the organism to cope with changes in the environment or other external stressors. However, excess stress—psychological or physical—is a well-recognized precedent of harm. Remarkably, the strain involved with critical illness, the perfect embodiment of a severe, prolonged stress, has received relatively little attention. Consideration of critical illness as a stress-related decompensation could prompt new treatment paradigms with a reevaluation of current management. The challenge is to discriminate when the stress response is turning into a destructive force. This article will cover various historical concepts of stress and its implications for critical care medicine.

ANTECEDENTS OF THE CONCEPT OF STRESS

Hippocrates (*ca*. 460–370 bc) described health as a balance of four basic humors: blood, black bile, yellow bile, and phlegm. Illness was due to a loss of equilibrium of these humors (*dyscrasia*) that could be overcome by reestablishing balance through the healing powers of nature (1). The Epicurean and Stoic schools determined that mind has a strong influence on health. *Apatheia* (absence of passion) and *ataraxia* (freedom from worry) represented a desirable state (1). Thomas Sydenham (1624–1689) considered the forces of the organism that try to overcome disease could actually cause the morbid state (1).

John Hunter (1728–1793) recognized a series of host responses that aided tissue repair and general recovery. He argued that surgeons should understand how the body adapted to and compensated for damage due to injury, disease, or environmental change. For example, he observed that untreated gunshot wounds often healed better than those subjected to the surgeon's knife (2). On the other hand, Hahnemann (1755–1843) considered disease to be a disturbance of the vital force, and that this force had the ability to react and adapt to internal and external factors (3). He presciently argued that conventional medicine did as much harm as good. Only correction of the underlying disturbance in the vital force could cure the disease.

THE FIRST CONCEPTS OF STRESS

The concept of stress was introduced by Robert Hooke (1635–1703) as a primary mechanistic term for certain physical principles (4). A body was elastic if it recovered its shape after deforming forces ceased. Hooke established a relationship between the deformation produced in a solid (ΔL) and the forces applied (F) by means of a proportional constant (K), where $F = k \Delta L$. This equation can be applied to biology where F represents stress forces (also known as stressors or, simply, stress) and ΔL (or strain) represents deformation of the body due to these stressors. For many years k has been considered a natural number, thereby establishing a linear relationship between stress forces and strain.

The term "strain" did not persist within biology as "stress" came to signify the

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Dr. Singer works at UCLH/UCL, which receives a proportion of its funding from the UK Department of Health's NIHR Biomedical Research Centre's funding scheme.

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e31826567eb

response of the body to different noxious loads or stressors. Stress was first used in the medical literature by Sir William Osler to express the physical problems he encountered in some overworked Jews (4). However, stress as a general term can be quite confusing. An individual is under stress when they are subject to the pressure of a stressor agent. Their reaction to this stressor is called "stress reaction" or strain, and this can be expressed either acutely or in a prolonged or chronic form. While mechanisms underlying both situations are similar, the consequences for the body may be quite different.

THE INTERNAL ENVIRONMENT AND HOMEOSTASIS

Claude Bernard (1813–1878) introduced the notion of a fixed internal environment (*milieu interieur*), whereby cells are maintained through continual compensatory changes of body functions (5). This was an essential condition for an independent and free life, with regulation occurring via the central nervous system. Walter Bradford Cannon (1871–1945) (6) adapted this concept and coined the term "homeostasis," referring to a set of acceptable ranges of values of internal variables. He argued that illness appeared when homeostatic systems failed to keep physiology within normal values, and the only state of equilibrium possible was that described by normality. Notably, the organ support paradigm used in current critical care practice uses devices and/or drugs to restore physiological variables back to (near-)normality (7). This "substitution strategy" used when homeostatic mechanisms fail may, as described later, carry unfortunate consequences (7, 8).

Cannon (9) also described the fight–flight response where, in the face of a stressor, blood flow increases to the brain, heart, lung, and skeletal muscles, but decreases to "nonessential" organs such as the gut. Sweating increases to cool the body, senses are heightened, pupils dilate, and vision focuses on threat or escape with the muscles ready to fight or flee (9). There may be a more comprehensive approach in mammals with a sequence of freeze, flight, fight, or fright (10).

EBB AND FLOW PHASES

David Cuthbertson (1900–1989) recognized that under traumatic stress the body uses protein from lean tissues (11). Patients with bone fractures had a much higher urinary elimination of intracellular constituents such as nitrogen, sulfur, phosphorus, potassium, and creatinine. He later described ebb and flow phases after traumatic stress. The ebb (shock) phase started immediately with a decrease in metabolic activity, subnormal oxygen consumption, increases in blood glucose, sodium retention, and tissue edema related to increased vascular permeability. The later flow (post-shock) phase, initially called traumatic inflammation (12), commenced after 3–10 days when an increased catabolic state produced a negative nitrogen balance with proteolysis and gluconeogenesis from amino acids and free fatty acids, and a decrease in fat stores. This phase ended when the healing process began, with metabolism then reverting to the anabolic state (13). While not necessarily an accurate representation of events, the ebb–flow concept has been used as a road map to guide resuscitation of shocked patients (14).

GENERAL ADAPTATION SYNDROME

Hans Seyle (1907–1982) conceived the General Adaptation Syndrome (15) with stress being a "nonspecific response by the body to any demand," physical or psychological. The General Adaptation Syndrome represents a "chronological development of the stress response to stressors when their action is prolonged." It consists of an initial "alarm reaction" or "shock" phase, a second stage of "resistance" or "contra-shock," and a final "exhaustion" stage (16). Selye felt the second phase was favorable as it opposed the shock phase, allowing the body to compensate and restore homeostasis (15). He demonstrated that the nonspecificity of the stress response was a universal finding, although he also recognized that some stressors elicited specific effects. He defined *eustress* (healthy stress) to differentiate a physiological response from *distress* (pathogenic stress). *Stress-induced maladies* could be produced by distress resulting from an excessive or inappropriate response to a stressor. Selye was puzzled by the apparent contradiction of the stress response being protective, yet still able to trigger diseases and pathology as a consequence of this adaptation. He also described a Local Adaptation Syndrome to accommodate evidence that local insults could trigger a stress response (15).

COGNITIVE STRESS

Lazarus and Folkman (1922–2002) adopted a nonbiological approach to the stress phenomenon in humans (4), emphasizing the importance of emotions, coping, and appraisal during the cognitive phase. A prophylactic psychological intervention to reduce presurgical stress could prevent a perioperative decrease in B lymphocyte cell counts (17). The coping mechanism has also been linked to the development of autoimmune diseases after adverse events (18).

Personality trait is a risk factor associated with the development of cardiovascular diseases. Aggressive type A personalities (hawks) are linked to larger catecholamine release against threats with an increase in the rate of malignant tachyarrhythmia and sudden death. The less irritable type B personalities (doves) typically respond with chronic hypercortisolemia and abnormalities such as metabolic syndrome, centripetal obesity, and hypertension (19).

THE DISHARMONIC REACTION

Laborit (1914–1995) (20) described an "oscillatory reaction post-aggression" or the "disharmonic reaction". He described the stress response as an initial depression or oxidative phase with an immediate collapse of the body, followed by a reaction or reductive phase (similar to Selye's contra-shock phase) and, finally, a terminal or new oxidative phase resulting in death of the organism. Unlike Selye, Laborit realized that the reaction phase was also part of the problem. He suggested that hyperglycemia, hyperlactatemia, acidosis, azotemia, and hypercoagulation were pathophysiological rather than homeostatic responses. He was highly concerned about the effects of catecholamines on the body during the reaction phase, considering sympathomimetics to cause many of the problems seen during shock states, as he demonstrated by infusing epinephrine into animals (20). He argued that the body needed a different homeostasis during the reaction phase. He called this phase "relative homeostasis" in contradistinction to the homeostasis present in health. This relative homeostasis could still damage the body if the insult was extremely violent or prolonged.

Laborit used chlorpromazine as a central and peripheral adrenergic inhibitor to prevent some of the changes seen during shock states, in particular vasoconstriction with its side effects related to organ

hypoperfusion. Chlorpromazine also stabilized cell membranes, preventing lysosomal rupture. He developed the concept of "artificial hibernation" with this neuroleptic agent as a means of controlling the stress response (20). His therapeutic approach was thus based on preservation of the disharmonic reaction while concurrently moderating the intensity and duration of local and general reactions to the stressor.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The Systemic Inflammatory Response Syndrome (SIRS) (21), the SIRS/CARS (Compensatory Anti-inflammatory Response Syndrome)/Mixed Antagonistic Response Syndrome model (22) and, more recently, the Predisposition, type of Insult, Response, and number of failing Organs concepts (23) offer different approaches to consider the stress phenomenon in the critically ill patient.

The SIRS model has been useful in articulating common criteria to define a systemic inflammatory response that is markedly similar for both infectious and noninfectious insults (24). Indeed, this nonspecificity emphasizes a common response pathway to an extrinsic stressor. That a patient could have some or all of the features of SIRS, yet not be critically ill, implies the basis for critical illness as a primitive response, with the stress response being a central component.

The SIRS/CARS/Mixed Antagonistic Response Syndrome model has redefined the concept of homeostasis as an equilibrium between forces generating pro- and anti-inflammatory responses (22). Patients can be primed to develop a multiorgan dysfunction syndrome by preexisting comorbidities (22), where the ability to cope with severe stress is diminished. Systemic inflammation can trigger multiorgan dysfunction syndrome, and this continuum of severity in turn affects prognosis. Organ dysfunction occurs when the body is no longer capable of maintaining homeostasis.

DYNAMICAL SYSTEMS (CHAOS) THEORY

Ludwig von Bertalanffy (1901–1972) suggested that a nonlinear, nonequilibrated process could provide stability. Networks (e.g., among cells, tissues, and organs) can jump from one stable state to another, providing "order for free." This concept suggests that multiorgan dysfunction syndrome could be the materialization of a network failure among cells, tissues, and organs (7). When applied to biology, this model, also known as dynamical systems (or chaos) theory, states that relationships between physiological variables are nonlinear but with marked connectivity and that small changes can result in major consequences (the "butterfly effect") (25).

ALLOSTASIS

Bruce McEwen revisited Selye's model (26), in particular, trying to understand the long-term effects of the physiological response to stress. The key element of this model is *allostasis*—"stability through change." This concept, developed by Sterling (27) and Eyer, refers to the active processes by which the body responds to daily events to maintain homeostasis—stability through constancy" (27).

McEwen paid particular attention to chronic stress. He explained Selye's eustress ("good stress") concept as an allostatic response, whereas distress ("bad stress") represented allostatic load or overload that causes Selye's (15) "diseases of adaptation" or "stress-induced maladies". Two types of allostatic overload have been described, acute (type I) and chronic (type II) (28). Type I overload is the stress response to different threats that increases the body's demand for energy beyond the point where supply cannot match it. This is the usual stress response in acute illness. On the other hand, many chronic stress-related diseases such as hypertension, stroke, obesity, metabolic syndrome, memory impairment, and autoimmune diseases have been related to a type II allostatic overload (26, 29). Here, allostatic load remains chronically high and does not trigger an escape or survival response, but can only be modified by changes in psychological and social structure (19). Both Selye and McEwen recognized the important role of the brain in initiating and regulating the stress response (15, 26).

EUSTASIS, DYSHOMEOSTASIS, AND HYPERSTASIS

George Chrousos (30) has offered another nomenclature to understand the stress response. *Eustasis* represents healthy homeostasis, while *dyshomeostasis* or *cacostasis* appears when the stress response produces an allostatic overload in the organism, resulting in negative consequences. *Hyperstasis* is a state the organism achieves after the stress response has adapted and improved the manner by which the body copes with the stressor (30).

Chrousos and Gold (1) described the activity of the stress system as a sigmoidal dose–response curve with stressor potency and stress response related in a nonlinear manner. This concept can be modified to show stressor potency as an independent variable and the stress response as the dependent variable (Fig. 1). The activity of the stress response will need a threshold to be activated (i.e., a resilience or vulnerability point), beyond which a quasilinear relationship commences. Beyond a further point, activity does not increase despite further increases in stressor potency (i.e., an allostatic overload point). This dose–response sigmoid curve is individual-specific and can display left or right shifts in hyperreactive or hyporeactive individuals, respectively (1).

THE STRESS SYSTEM

The stress system has been described in detail (1, 31, 32). Figure 2 offers a simple representation of its complexity.

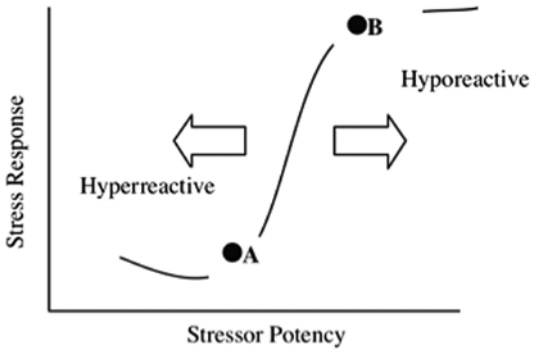

Figure 1. A sigmoid stress response (adapted with permission from Chrousos and Gold [1]). *A*, resilience point; *B*, allostatic overload point.

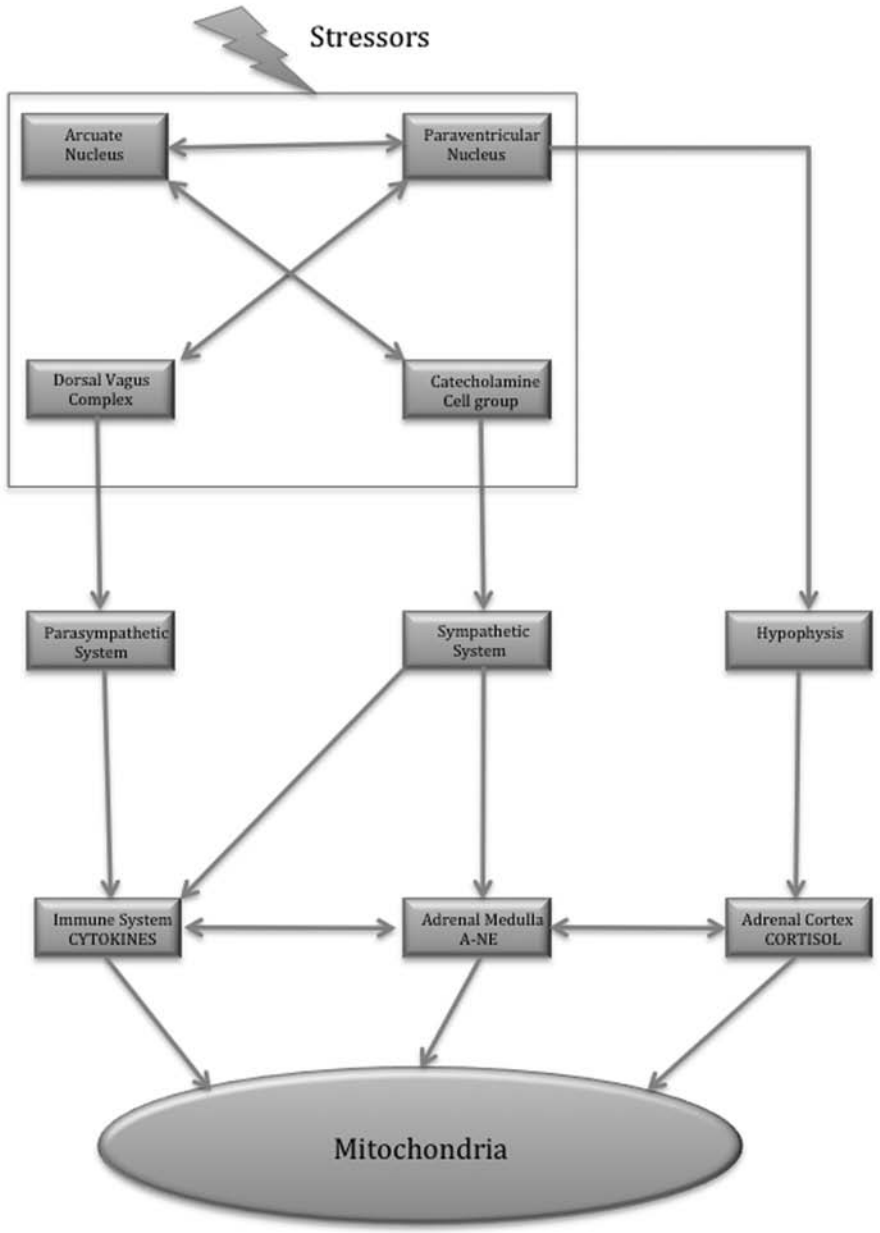

Figure 2. The stress system. The central stress system is shown within the rectangular box. *A*, adrenaline; *NE*, norepinephrine (modified from [30, 32]).

It is organized into central, peripheral, and cellular systems within a network of anatomical regions that work together to keep the body both informed and ready to react to changes in either external or internal cellular environments.

The primitive brain (diencephalon and brainstem) is the system's core and termed the "*central stress system*." Afferent signals come from sensory receptors and somatosensorial ascending fibers situated both externally on the skin, internally on any other tissue, and from the prefrontal cortex (related to cognition), limbic system (for emotion), and hippocampus (for memory).

The peripheral elements of the network consist of pituitary gland, parasympathetic and sympathetic nervous system, adrenal glands, and immune cells. Interaction among the sympathetic, parasympathetic, and immune systems releases cytokines. Secretion of cortisol, adrenaline, and cytokines is mutually interconnected, with both positive and negative feedback systems that generate an adequate stress response to the insult.

Mitochondria act as a common pathway and are considered the principal cellular stress system (33). Apart from providing most of the body's energy requirements, they have numerous other functions including crucial roles in lipid metabolism, calcium regulation, intracellular signaling, and initiation of cell death pathways. Short-term exposure to stress cytokines and hormones (e.g., cortisol, adrenaline, and noradrenaline) increases substrate availability, ATP production, thermogenesis, and mitochondrial protein turnover (biogenesis) (34). However, excessive acute or chronic exposure to the same cytokines and hormones has the opposite effect, as well as increasing production of radical oxygen species (35). The enhanced oxidizing environment within the cell may also contribute to mitochondrial and nuclear DNA damage and the induction of cell death (apoptosis or necrosis) pathways (33).

Differences in genetic variations of mitochondrial DNA (mtDNA haplogroups) could explain individual susceptibilities to stress. These haplogroups likely vary in their oxidative phosphorylation efficiency and in their ability to generate protective antistress proteins or chaperones (i.e., heat shock proteins). For example, haplogroup H confers a mitochondrial phenotype of increased electron transport chain activity and additional heat generation. This likely offered an evolutionary advantage in cold climates. Although the newest of the European haplogroups, it is the most common and may offer a survival advantage in sepsis (36). A similar advantage is reported in Han Chinese with haplogroup R (37).

Ischemic preconditioning (an adaptive response or hormesis) can enhance mitochondrial protective mechanisms against stress. First described in the heart, where an ischemic stimulus insufficient to damage the tissues could increase the cell's ability to survive a subsequent potentially lethal insult (38), it has since been reported in virtually every body tissue. Any potentially harmful stimulus can elicit a preconditioning effect (39). It may thus represent a fundamental self-preservation mechanism against stressors such as hypoxemia, ischemia, infection, exercise, and dietary restriction. This may explain why patients with transient ischemic attacks fare better with later major ischemic events. Furthermore, aggressive clinical treatment after this preconditioning stimulus (as happens after transient ischemic attacks in some patient populations) could even be harmful (40).

STRESS-RELATED CHANGES IN ORGAN MORPHOLOGY

Selye's (16) classical description revealed specific macroscopic and microscopic

changes in multiple organs throughout the body after a variety of acute psychological, physiological, and pharmacological insults in laboratory rats. Findings in stressed humans are not necessarily the same due to the variability in disease process, illness trajectory, and time of presentation, plus differences in age, gender, comorbidity, long-term medication, and so forth. However, some stress-related changes in humans have specific features that are characteristic of the insult. A classical example is Takotsubo (stress) cardiomyopathy where, despite normal coronary arteries, the heart manifests contractile dysfunction that changes the shape of the left ventricle to that of an octopus pot. The trigger is usually psychological (e.g., bereavement), but can follow physical stress. Histology shows infiltration of lymphocytes and macrophages with or without contraction-band myocyte necrosis (41). Plasma catecholamines are markedly elevated, and the condition responds effectively to β-blockade.

Morphological changes in multiorgan failure reveal a marked discrepancy between the minimal macroscopic findings seen at postmortem compared to the degree of organ dysfunction present before death (42). A plausible explanation of this paradox is derived from changes in mitochondrial structure and function following acute stress. The apoptotic theory suggests that increased mitochondrial generation of reactive oxygen species after an acute insult could lead to apoptosis (43), whereas the hibernation theory states that organs are protected from death or irreversible failure by a metabolic shutdown analogous to the hibernation response found in wintering mammals (44). When the stress response is potentially overwhelming, a low energy status is generated within the cell accounting for measurable organ dysfunction (45). These two theories need not be mutually exclusive; both metabolic shutdown and apoptosis are parts of the hibernating cycle of some mammals (46).

RESPONSES TO ACUTE ILLNESS

Wilmore (11) described two schools of thought for understanding the stress response in critical illness. Traditionalist thinking envisages the stress response as a "good force" providing homeostatic adaptation to illness. The Modernist School however argues that necessary interventions are those that modify the stress response to attenuate or prevent its undesirable features (i.e., organ failure). A corollary of the Modernist School is the striving for normality with benefit from sustaining normal biological values within normal values usually considered "safe." A third "Post-Modernist" school can be added that attempts to strike a balance between these extremes and which embraces the essential concept of allostasis (27).

Current intensive care practice is based on maintaining the constancy of the internal environment. Indeed, Claude Bernard declared constancy to be the sole object of all vital mechanisms. Nevertheless, the allostatic concept emphasizes that the brain predicts the most likely demand during a stress response, and therefore modifies physiological variables to values that match anticipated demand. Healthy physiological values routinely targeted in the critically ill are not related to these anticipatory demands and are thus likely to be inappropriate. Furthermore, treatments aimed at normalizing physiology may trigger a cascade of downstream effects. Thus, a drug can modify a brain signal against which the brain may attempt to compensate by driving other signals harder. Alternatively, the drug may clamp a variable to such an extent that it decreases the performance of a physiological system (27).

The endocrine–metabolic response is a perfect exemplar of the above. Corticosteroid therapy for severe sepsis has oscillated in and out of fashion (47), yet with little consideration being paid to its impact on the individual patient. The large anti-inflammatory doses of the 1970s–1980s were replaced by more judicious "replacement" dosing during the 2000s. However, little cognizance has been made of the magnitude of inflammatory response in an individual patient, nor the degree of dosing necessary to achieve a sufficient but not excessive effect. Sicker, decompensated patients tend to show benefit whereas the less sick do not (48).

The intrinsic sympathoadrenal response will be modified by the exogenous use of catecholamines. Their side effects, cleverly anticipated by Laborit (20), such as tachyarrhythmia, digital ischemia, stimulation of bacterial growth, immunosuppression, thrombogenicity, decreased bioenergetic efficiency, increased cardiac work, and ventricular remodeling, argue against their current use in shock states (49). The use of β-blockers or α^2-adrenergic blockers may prove an important option in some intensive care scenarios (50, 51); however, use of such agents is also not risk-free (52).

The intensive care environment itself is also a major contributor to the stress response to critical illness. Among other factors, noise, sleep deprivation, loss of circadian rhythms, lack of natural light, and loss of entitlement increase the stress load (19).

A GENERAL UNIFIED THEORY OF STRESS AND APPLICATION TO A NEW ICU MANAGEMENT PARADIGM

The stress response can be described as the universal response of all living cells that mobilizes both short- and long-term allostatic forces. This model is based on the three historically described phases of the stress response (Table 1). Targeted modification of each phase, taking into consideration the natural history of critical illness and the concept of allostasis, may positively impact on the management and outcomes of the critically ill.

During the initial phase of the stress response (acute phase of critical illness, phase I), the aim of treatment is to prevent derangement of normal physiological values. This embraces the concept of the golden hour to restore physiology and prevent organ dysfunction (53).

Once organ failure has become established (established phase of critical illness, phase II), therapy should be directed toward a strategy that supports the intrinsic cellular mechanisms of protection and tolerance that develop during the initial phases of the stress response.

Table 1. Phases I, II, and III of the stress response, according to different authors

Author (Ref)	I	II	III
Cannon (9)	Flight	Fight	Fright
Cuthbertson (11)	Ebb	Flow (initial)	Flow (late)
Selye (15)	Shock	Contra-shock	Exhaustion
Laborit (20)	Depression	Reaction	Terminal
Bone et al (21, 22)	Systemic inflammatory response syndrome	Multiorgan dysfunction syndrome	Recovery/death
McEwen (26)	Allostatic response	Allostatic state	Allostatic overload
Chrousos (30)	Eustasis	Dyshomeostasis	Hyperstasis

Pathophysiological responses should thus not be considered simply as disturbances of physiology, but as factors that accommodate the body to the insult. Permissive values of hypercapnea, hypoxemia, hypotension, oliguria, and anemia, among others, could be beneficially targeted. However, acceptable ranges must be defined, acknowledging these will be patient-specific and likely to change over time. The benefit of this approach will be a decrease in iatrogenically related deterioration that represents perhaps the most important single burden in modern intensive care (54). It may also be possible to decrease the anticipatory demand of the brain by directly decreasing its activity, e.g., using a hibernatory approach (55), or by vagally stimulating the cholinergic anti-inflammatory parasympathetic pathway (32) to readapt the stress response while maintaining responsiveness.

Finally, when the patient improves (recovery or repair phase of the critical illness, phase III), normal (healthy) physiological values could be progressively reintroduced as therapeutic targets.

Patients often fail to follow a linear progression in their clinical condition, but rather oscillate dynamically between the phases schematically described above. This oscillation may be precipitated in part by the maladaptive effects of therapies being given. Interventional pharmacological and mechanical supports may frequently be considered as stressor agents in their own right; their interaction with the human body can be associated with a stress response that may even supersede the existing stress response from the acute insult.

For the clinician to individualize and optimize treatments in relation to the phase of the patient's critical illness, the molecular mechanisms underlining each stage will need to be determined using novel techniques such as real-time functional genomics, proteomics, and computer modeling (56). Making such a distinction between the different phases of the stress response may also help to adjust current therapies. When a patient is consciously able to interact, particular attention needs to be paid to his/her environment, such as good natural light and noise reduction, as well as nonpharmacological maneuvers that can improve healing and sleep patterns and decrease anxiety, such as communication, reassurance, empowerment, music therapy, massage, or even animal-assisted therapy (57).

A modified Hooke's equation to represent the stress response:

$$F_n = \int_{t_i}^{t_f} \rho(t_n) \cdot L(t_n) \cdot dt$$

Resilience (ρ) is a concept that could usefully summarize the interaction among predisposition factors (such as genes, age, comorbidities, and physiological reserve), the injury (or stressors), and the body's allostatic responses. The magnitude of ρ describes how the brain meets, or fails to meet, the evolving needs of the stress reaction. Hooke's classical equation could be rewritten as $F = \rho\, \Delta L$, where ρ could be any number (or mathematical function), and not just a natural number. This opens up the opportunity of understanding the stress response in a nonlinear fashion with heuristic implications for critical care (7, 25). Indeed, stressor-specific pathways may exist that could label some stressors with a characteristic biological signature (58).

A revisited presentation of the Hooke equation may help to close the knowledge gaps that still remain with respect to stress. In effect, F_n could represent a particular stress force (e.g., infection), and this could be related to time, as described in the equation. In this equation, F_n *is* the force generated by a stressor, $\rho(t_n)$ is the resilience factor associated with that particular stressor at a particular timepoint, and $L(t_n)$ is the response of the body (i.e., strain) related to both time and stressor. Theoretically, F_n can be computed if all modifications of ρ and L that occur over the duration of action of the stress force are known. ρ may be potentially derived from mitochondrial oxygen uptake while L could be calculated using body deformation as measured by an organ failure score. The value of F generated may prove a useful predictor of outcome, a means of building a more individual approach when studying research questions in large samples, and a tool to select and titrate treatment.

CONCLUSIONS

The stress response is a preexisting behavioral mode of all living cells released by the brain in a bundle of adaptive responses. The stress response can induce major adaptive and protective cellular mechanisms; however, a deleterious consequence may be organ dysfunction and failure. Critical illness may thus represent a stress-related decompensation syndrome. Better understanding of the beneficial and harmful effects of the stress response, including its potential quantitation through computation of resilience, may improve patient care and outcomes through modifications in physiological, pharmacological, and psychological support.

ACKNOWLEDGMENT

We thank Celia M. Madrigal, Physics Undergraduate at University College London, who devised the integer from Hooke's equation.

REFERENCES

1. Chrousos GP, Gold PW: The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 1992; 267:1244–1252
2. Moore W: John Hunter: Learning from natural experiments, 'placebos', and the state of mind of a patient in the 18th century. *J R Soc Med* 2009; 102:394–396
3. Schmidt JM: The concept of health—In the history of medicine and in the writings of Hahnemann. *Homeopathy* 2010; 99:215–220
4. Lazarus RS, Folkman S: Stress, Appraisal and Coping. New York, Springer-Verlag, 1984
5. Bernard C. Leçons sur les phénomènes de la vie communs aux animaux et aus végétaux. Vol. 1. Paris, Baillère, 1878. Available at: http://www.archive.org/stream/leonssurlesph01bern/leonssurlesph01bern_djvu.txt. Accessed September 1, 2011
6. Cannon WB: The Wisdom of the Body. New York, WW Norton, 1932
7. Buchman TG: The community of the self. *Nature* 2002; 420:246–251
8. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
9. Cannon WB: Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches into the Function of Emotional Excitement. New York and London, D. Appleton, 1915
10. Bracha HS, Ralston TC, Matsukawa JM, et al: Does "fight or flight" need updating? *Psychosomatics* 2004; 45:448–449
11. Wilmore DW: From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Ann Surg* 2002; 236:643–648
12. Campbell RM, Cuthbertson DP, Pullar JD: The effects of betamethasone and fracture on nitrogen metabolism. *Q J Exp Physiol Cogn Med Sci* 1964; 49:141–150
13. Cuthbertson DP: Second annual Jonathan E. Rhoads Lecture. The metabolic response to injury and its nutritional implications: Retrospect and prospect. *JPEN J Parenter Enteral Nutr* 1979; 3:108–129
14. Sibbald WJ: Shockingly complex: The difficult road to introducing new ideas to critical care. *Crit Care* 2004; 8:419–421

15. Selye H: Forty years of stress research: Principal remaining problems and misconceptions. *Can Med Assoc J* 1976; 115:53–56
16. Selye H: A syndrome produced by diverse noxious agents: 1936. *J Neuropsych Clin Neurosci* 1998; 10:230–231
17. Garcia MI, Cuesta JM, Vitaller AR, et al: Response to presurgical stress in outpatients surgery: Effects on lymphocyte populations of a psychological treatment to prevent surgical anxiety. *Rev Esp Anestesiol Reanim* 2005; 52:383–388
18. Karaiskos D, Mavragani CP, Makaroni S, et al: Stress, coping strategies and social support in patients with primary Sjögren's syndrome prior to disease onset: A retrospective case-control study. *Ann Rheum Dis* 2009; 68:40–46
19. Brame AL, Singer M: Stressing the obvious? An allostatic look at critical illness. *Crit Care Med* 2010; 38(10 Suppl):S600–S607
20. Laborit H: [General biological basis of reaction to aggression]. *Agressologie* 1972; 13:1–54
21. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
22. Bone RC, Grodzin CJ, Balk RA: Sepsis: A new hypothesis for pathogenesis of the disease process. *Chest* 1997; 112:235–243
23. Levy MM, Fink MP, Marshall JC, et al; International Sepsis Definitions Conference: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med* 2003; 29:530–538
24. Dulhunty JM, Lipman J, Finfer S; Sepsis Study Investigators for the ANZICS Clinical Trials Group: Does severe non-infectious SIRS differ from severe sepsis? Results from a multi-centre Australian and New Zealand intensive care unit study. *Intensive Care Med* 2008; 34:1654–1661
25. Seely AJ, Christou NV: Multiple organ dysfunction syndrome: Exploring the paradigm of complex nonlinear systems. *Crit Care Med* 2000; 28:2193–2200
26. McEwen BS: Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiol Rev* 2007; 87:873–904
27. Sterling P: Principles of allostasis: Optimal design, predictive regulation, pathophysiology, and rational therapeutics. *In:* Allostasis, Homeostasis, and the Cost of Physiological Adaptation. Schulkin J (Ed.). Cambridge, UK, Cambridge University Press, 2004, pp 17–64
28. McEwen BS, Wingfield JC: The concept of allostasis in biology and biomedicine. *Horm Behav* 2003; 43:2–15
29. McEwen BS: Stressed or stressed out: What is the difference? *J Psychiatry Neurosci* 2005; 30:315–318
30. Chrousos GP: Stress and disorders of the stress system. *Nat Rev Endocrinol* 2009; 5:374–381
31. Chrousos GP: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995; 332:1351–1362
32. Tracey KJ: Reflex control of immunity. *Nature* 2002; 420:853–859
33. Manoli I, Alesci S, Blackman MR, et al: Mitochondria as key components of the stress response. *Trends Endocrinol Metab* 2007; 18:190–198
34. Duncan JG, Fong JL, Medeiros DM, et al: Insulin-resistant heart exhibits a mitochondrial biogenic response driven by the peroxisome proliferator-activated receptor-alpha/PGC-1alpha gene regulatory pathway. *Circulation* 2007; 115:909–917
35. Bourgeois JM, Tarnopolsky MA: Pathology of skeletal muscle in mitochondrial disorders. *Mitochondrion* 2004; 4:441–452
36. Baudouin SV, Saunders D, Tiangyou W, et al: Mitochondrial DNA and survival after sepsis: A prospective study. *Lancet* 2005; 366:2118–2121
37. Yang Y, Shou Z, Zhang P, et al: Mitochondrial DNA haplogroup R predicts survival advantage in severe sepsis in the Han population. *Genet Med* 2008; 10:187–192
38. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; 74:1124–1136
39. Bolli R: Preconditioning: A paradigm shift in the biology of myocardial ischemia. *Am J Physiol Heart Circ Physiol* 2007; 292:H19–H27
40. O´Duffy AE, Bordelon YM, McLaughlin B: Killer proteases and little strokes-how the things that do not kill you make you stronger. *J Cereb Blood Flow Metab* 2007; 27:655–668
41. Wittstein IS, Thiemann DR, Lima JA, et al: Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; 352:539–548
42. Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; 348:138–150
43. Bayir H, Kagan VE: Bench-to-bedside review: Mitochondrial injury, oxidative stress and apoptosis–There is nothing more practical than a good theory. *Crit Care* 2008; 12:206
44. Singer M: Mitochondrial function in sepsis: Acute phase versus multiple organ failure. *Crit Care Med* 2007; 35(9 Suppl): S441–S448
45. Singer M, De Santis V, Vitale D, et al: Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 2004; 364:545–548
46. Yan J, Barnes BM, Kohl F, et al: Modulation of gene expression in hibernating arctic ground squirrels. *Physiol Genomics* 2008; 32:170–181
47. Vincent JL: Steroids in sepsis: Another swing of the pendulum in our clinical trials. *Crit Care* 2008; 12:141
48. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327
49. Singer M: Catecholamine treatment for shock–Equally good or bad? *Lancet* 2007; 370:636–637
50. Herndon DN, Hart DW, Wolf SE, et al: Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001; 345:1223–1229
51. Riker RR, Shehabi Y, Bokesch PM, et al; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group: Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA* 2009; 301:489–499
52. Devereaux PJ, Yang H, Yusuf S, et al; POISE Study Group: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. *Lancet* 2008; 371:1839–1847
53. Smith G: Acute Life-threatening Events Recognition and Treatment (ALERT). Second Edition. Portsmouth, University of Portsmouth, 2003
54. Singer M: The key advance in the treatment of sepsis in the last 10 years.doing less. *Crit Care* 2006; 10:122
55. Wagner F, Asfar P, Calzia E, et al: Bench-to-bedside review: Hydrogen sulfide–The third gaseous transmitter: Applications for critical care. *Crit Care* 2009; 13:213
56. Hopf HW: Molecular diagnostics of injury and repair responses in critical illness: What is the future of "monitoring" in the intensive care unit? *Crit Care Med* 2003; 31(8 Suppl):S518–S523
57. Tracy MF, Chlan L: Nonpharmacological interventions to manage common symptoms in patients receiving mechanical ventilation. *Crit Care Nurse* 2011; 31:19–28
58. Pacák K, Palkovits M: Stressor specificity of central neuroendocrine responses: Implications for stress-related disorders. *Endocr Rev* 2001; 22:502–548