Stressing the obvious? An allostatic look at critical illness

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Stress plays a crucial role in coping with extrinsic insults through modulating the autonomic nervous system, the hypothalamic-pituitary-adrenal axis and the cardiovascular, metabolic, and immune systems. The allostatic model of maintaining "stability through change" allows the body to respond to a challenge by adjusting to a new steady-state and terminating it once the danger has passed. However, unrelenting stress can lead to decompensation with development of pathologic illness. With sufficient activation the response may become more damaging than the stressor itself. Two types of "allostatic overload" are described: type 1 is an essentially protective response triggered by changes in environment, food supply, or physiologic status where energy demand exceeds supply. The response aims to reduce this imbalance by modifying behavior and intrinsic body systems to direct the animal into a survival mode. Type 2 overload occurs when there is sufficient or excess energy consumption; however, this situation does not trigger an escape or survival response. A clear analogy may be made to critical care where excess stress affects metabolic, hormonal, and immunoinflammatory responses and contributes to the development of organ failure. Ongoing stress also compromises recovery so it is incumbent upon caregivers to reduce stress, be it induced by tissue hypoxia, catecholamine infusion, sleep deprivation, pain, anxiety, and/or excess noise. (Crit Care Med 2010; 38[Suppl.]:S600–S607)

KEY WORDS: stress; allostasis; allostatic load; overload; homeostasis; catecholamines; corticosteroids; dysregulation; sympathetic drive; inflammation

The *milieu intérieur* (the "environment within") was coined by Claude Bernard in 1852 to refer to the extracellular fluid environment and its physiologic capacity to ensure protective stability for the body's tissues and organs. Although only concerned initially with the role of the blood in ensuring this internal stability, Bernard later expanded his views to encompass the whole body (1): "The fixity of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated . . . . All of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment … the constancy of the internal environment is the condition for free and independent life."

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As well as investigating physiologic mechanisms that enable such internal constancy, Bernard also examined its breakdown under duress. His ideas were both revolutionary and controversial. Debate raged as to whether the disease was produced by the organism itself (Pasteur's germ theory) or, as Bernard maintained, arose from inappropriate or inadequate responses by the body, regardless of actual threat. William Osler observed that a person's "material condition" rendered them "more or less immune" and offered the analogy of tuberculosis where the "soil then has a value equal almost to that which relates to the seed" (2).

Today, it is increasingly recognized that diseases stem from interactions among genetics, environment, threat, and response. However, in Bernard's time, the concept of stressors contributing to the pathophysiology of disease was a novel departure. Walter Cannon introduced the paradigm of the acute stress response in 1915, whereby animals react to threats with a general discharge of the sympathetic nervous system, priming the animal to fight or flee. Cannon subsequently published *The Wisdom of the Body* in 1932, in which he describes the concept of homeostasis, based on Bernard's milieu interieur concept. Homeostasis demands that each internal physicobiochemical variable is maintained within a relatively narrow set-point range by sensing and correcting perturbations via negative feedback. Homeostasis maintains the physiologic stability of systems imperative to survival such as temperature, pH, osmolality, and glucose level. However, homeostasis as a concept is limited to negative feedback loops and defined set-points and does not consider the networked interaction between variables through which stability is achieved. Cannon's work focused on the adaptive response to stressors. He considered this response in a primarily positive light, although, he did note limits to this system through observing nervous exhaustion in soldiers fighting on the Western Front that was often manifest as physical illness. Subsequent work has confirmed that stressful events can induce both acute and chronic physical and psychiatric illness. The impact of stress on both critical illness and recovery forms the direction of this article, with reference made to current concepts of management of the acutely sick patient. The concept of allostasis and allostatic overload will be introduced as an important model to encourage active consideration of a philosophical redirection of the way we comprehend and treat critical illness.

The stress response–crucial for survival

Stability can be considered key to the maintenance of body function but this

has to be achieved without excessive taxation of available resources. The body mainly relies on physiologic mechanisms for first-line defense; breakdown develops when these are pushed beyond their regulatory and compensatory capacities.

The response to stress is dictated by a combination of stimulus, genetic predisposition, development, and perception. Any challenge can be judged as either threatening or benign. A perceived threat demands a response that may be neural, neuroendocrine, immune, cardiovascular, metabolic, and/or bioenergetic.

The autonomic nervous system has sympathetic and parasympathetic components that work in synchrony to maintain balance within the body. Autonomic function controls heart rate, blood pressure, breathing, temperature, gastrointestinal motility, and other essential functions and interacts with the limbic system (responsible for memory), brainstem, and hypothalamus (3). Acute stress results in noradrenergic discharge as well as increased secretion of noradrenaline and adrenaline from the adrenal medulla–the "adrenaline rush"—to prepare the organism to cope with an impending or current emergency and to enhance memory for future avoidance or anticipatory preparation (Table 1). Importantly, blood vessels and most endocrine cells are richly innervated by adrenergic nerve fibers. This allows the brain close access to virtually every somatic cell so it can act as the command center utilizing body systems to deal with stress through neuroendocrine control. As examples, parasympathetic nerves are in contact with pancreatic β cells to regulate insulin release, and with splenocytes that serve inflammation and immune surveillance (3).

The endocrine response to stress involves a shift in anterior pituitary hormone production in favor of adrenocorticotrophic hormone production. Increased release of glucocorticoids will initially stimulate the adrenal medulla to further increase adrenaline synthesis and release (4). The central nervous system receives sensory input from the immune system via both humoral and neural routes. The presence of bacteria or tissue damage activates the innate immune system to induce local release of cytokines and other mediators. Low amounts of tumor necrosis factor contribute to an appropriate host response by limiting spread of pathogenic bacteria through promoting neutrophil recruitment and local coagulation, and growth of damaged tissue. In a successful response to an extrinsic challenge, this cytokine release is appropriate in both duration and amount, and the effects are limited (3). However, a prolonged and/or severe local proinflammatory response with overspill into the systemic circulation results in widespread activation of defense pathways. This will trigger excessive sympathetic activation and adrenal medullary stimulation and a systemic inflammatory response that may lead to organ dysfunction and death. To prevent this from being a commonplace occurrence, the body has evolved sophisticated mechanisms to control the spread of infection and to quench the flames of systemic inflammation. This includes activation of anti-inflammatory hormones, cytokines and mediators (e.g., cortisol, interleukin-10, and prostacylin) and an increase in parasympathetic activity. Local inflammation activates sensory fibers ascending to the nucleus tractus solitarius, the area postrema, and the dorsal motor nucleus of the vagus. This leads to increased vagal efferent outflow that suppresses peripheral cytokine release through macrophage nicotinic receptors and the cholinergic anti-inflammatory pathway. Direct stimulation of the vagus, or downstream nicotinic receptors, will inhibit proinflammatory cytokine production in liver and heart after ischemic or endotoxemic challenge (3).

Table 1. Acute response to stress

- Adrenaline, cortisol, etc. released into bloodstream
- Liver begins breaking down glycogen to glucose for immediate energy boost
- Blood flow increases to brain, heart, lungs, and large muscles
- Flow decreases to lower priority organs such as gut
- Heart rate increases, blood pressure rises
- Breathing more shallow and rapid, and bronchioles dilate, to obtain more O_2
- Perspiration increases to keep cool
- Senses heightened and pupils dilate to let in more light
- Vision focuses on threat or escape route
- Auditory exclusion
- Muscles become tensed, ready to fight or flee
- Spleen releases leukocytes and platelets for possible injury
- Thrombogenicity

The stress response: a major contributor to harm

Stress that is prolonged, repetitive or that fails to switch off can, in itself, be detrimental. Table 2 highlights the pleiotropic effects of long-term excess of circulating catecholamines. For example, after an initial period of leukocytosis and activation of the reticuloendothelial system with increased phagocytosis and antibody formation, the phenotype changes markedly to one of immunosuppression (5). In combination with their ability to stimulate bacterial growth, (6) catecholamines may thus enhance the likelihood of developing secondary infection and further bouts of inflammation. Likewise, their role in utilizing substrate for energy provision includes breakdown of muscle to enable release of alanine and lactate. These are important fuel sources, particularly when glucose and glycogen stores are depleted. Although beneficial in the short-term, the loss of muscle bulk and strength may be an important factor in delaying or even preventing recovery from critical illness (7).

Table 2. Deleterious effects of catecholamines

- Arrhythmias
- Digital ischemia
- Increased cardiac work and decreased efficiency
- Myocardial necrosis
- Oxidative damage
- Metabolic modulation (insulin resistance, hyperglycemia, lipolysis)
- Immunomodulation
- Stimulation of bacterial growth
- Muscle catabolism

Before covering the detrimental effects of stress in critical care in more detail, it is instructive to highlight a number of stress-related illnesses recognized in other specialties, ranging from cardiology to neuropsychiatry.

Stress-related Cardiovascular Syndromes. Chronic psychological stress results in hypertension, ventricular hypertrophy, hyperlipidemia, accelerated atherosclerosis, and increased reactivity of fibrinogen and platelets, all of which magnify the risk of myocardial infarction. Raised levels of catecholamines also increase the risk of arrhythmias and sudden death. Notably, personality type plays an important role in determining the cardiovascular manifestations of stress. Type A "hawk-like" personalities are aggressive, hostile, and competitive and possess higher circulating levels of testosterone and catecholamines. Aggressive male rats have higher blood pressures compared to passive animals and are more likely to develop accelerated coronary and systemic atherosclerosis. Such animals have

higher baseline levels of noradrenaline and develop larger catecholamine responses to threat (8). This shift of autonomic nervous function toward sympathetic dominance is also associated with malignant tachyarrhythmias and sudden death (9). Profound sympathetic activation induces endothelial injury and abnormal increases in platelet accumulation, predisposing to clot formation (10). Chronic sympathetic nervous system activation and reduced parasympathetic antagonism has been observed in type A men (11); this may account, in part, for their increased prevalence of cardiovascular disease.

While passive, nonhostile "doves" are less irritable by nature and lack a high sympathetic load, they are also not immune to cardiovascular disease. Being more prone to emotional and depressive disorders, doves typically respond with increased activation of the hypothalamic-pituitary-adrenal (HPA) axis rather than sympathetic discharge. Chronically elevated cortisol results in impaired insulin resistance and raised circulating insulin levels, thus promoting deposition of body fat, obesity, and dyslipidemias. Combined with inactivity, a typical finding in passive doves, this increases the risk of further metabolic abnormalities. The metabolic syndrome is a cluster of conditions including insulin resistance, hyperglycemia, hypertriglyceridemia, decreased high-density lipoprotein cholesterol, centripetal obesity, and hypertension. Therefore, doves are also vulnerable to atherosclerosis.

A specific cardiovascular condition merits more detailed description. Reports of "dying from a broken heart" and being "frightened to death" are not merely the fanciful domain of fiction writers. The entity of stress-induced cardiomyopathy was first reported in Japan as recently as 1990 (12). Patients can present with chest pain or heart failure and while electrocardiographs may appear ischemic and cardiac enzymes elevated, angiography is usually normal. There is left ventricular dysfunction with wall motion abnormalities, and the left ventricle typically resembles a flask with a short neck and fat body. As befitting its Japanese origins, this appearance is called Takotsubo (octopus pot) cardiomyopathy. This condition is associated with substantial increases in plasma catecholamine levels (up to 34 times basal) (13), resulting in cardiac dysfunction akin to stunning. Watanabe et al (14) described a disproportionate rise in the rates of both sudden death and Takotsubo cardiomyopathy in the weeks following an earthquake in survivors who were psychologically traumatized but physically unharmed. Likewise, it can occur after sudden physical stress. Indeed, up to 10% of individuals with acute neurologic injury (e.g., head trauma and acute intracranial hemorrhage) have ischemic electrocardiogram changes, impaired left ventricular function, and elevated enzymes (15). Histology reveals leukocyte infiltration and contraction-band necrosis. Similar changes can also be seen in pheochromocytoma, in those who die under terrifying circumstances (e.g., fatal asthma), and in experimental models of heart failure driven by catecholamine infusions. These findings support the theory of adrenaline-mediated cardiomyocyte stunning. Possible mechanisms include down-regulation of β_1 adrenoceptors with switching toward the more negatively inotropic β_2 phenotype. Although potentially cardioprotective through counteracting the proapoptotic effect of a high catecholamine burden, this may be at the expense of reduced contractility. Catecholamines are also a potential source of oxygen-derived free radicals causing direct myocyte injury (13). Furthermore, catecholamines are implicated in causing epicardial spasm, microvascular dysfunction, and hypertrophy with outflow tract obstruction.

Of note, Takotsubo cardiomyopathy is far commoner (>90%) in women (16) whose basal and stress-induced adrenaline levels are generally much lower than men who generate higher levels in response to stress. Furthermore, estrogen reduces the changes in gene expression mediated by adrenergic receptor stimulation. Men also appear to be more sensitive to catecholamine-mediated vasoconstriction. As a result, they can develop more intense acute cardiotoxicity after a catecholamine surge, resulting in a fatal event, whereas women appear to be more vulnerable to sympathetically mediated cardiac stunning and cardiomyopathy. Interestingly, the syndrome is rapidly reversible within days to weeks, providing no further stressful events occur. β-Blockade has been used effectively as a therapeutic strategy in this condition (13) and also in reducing myocardial injury after isolated head trauma (17). However, β-blockade may also induce stimulus trafficking and potentiate the negatively inotropic state, thus possibly worsening the clinical situation (18).

Stress-related Neurologic Syndromes. Repeated stress affects brain function, especially in the hippocampus, which has a high concentration of cortisol receptors. Acute stress elevates adrenal steroids and adrenaline output and promotes and improves memory temporarily to promote survival in the acute event. These effects are usually short term; however, repeated or prolonged stress induces excitatory amino acids and glucocorticoid-driven atrophy of pyramidal dendrites, decreased dendritic branching in the hippocampus, and reduced neuronal numbers in the dentate gyrus (16, 17). Prolonged stress can permanently destroy hippocampal tissue; indeed, hippocampal atrophy is seen on imaging in stress-related disorders such as depression, post-traumatic stress disorder, and Cushing's syndrome (18). Long-term stress is also associated with "weathering" or accelerated aging as persistent excitatory amino acid and glucocorticoid release may potentiate atrophy and neuronal loss, leading to memory impairment and an enhanced fear response via neuronal remodelling. Adrenergic cells in the brainstem also send forward projections to the fore- and midbrain where adrenaline is released, interacting with α-adrenergic$_{1b}$ receptors that are in close proximity to dopaminergic, serotonergic, and noradrenergic neurotransmitter centers implicated in psychiatric illness. This may explain some of the psychological and behavioral consequences of sympathetic overload.

In humans, the maladaptive response to stress can outlast the actual stress phase by months or even years. Endocrine and behavioral effects evoked by stress can persist even if the stress is discontinued (19). These early experiences may set the level of responsiveness of the HPA axis and autonomic nervous system such that animals either over-react to minimal stress or, conversely, under-react, again causing potential harm.

Stress-related Respiratory Disorders. Resistive breathing represents a stressful challenge encountered in disease states, such as asthma and chronic air flow limitation, that are associated with airway inflammation and cytokine load. Strenuous breathing induces release of proinflammatory cytokines. This leads to respiratory muscle fatigue, structural injury, and also protein degradation, which is responsible in part for the wasting seen in chronic disease (20). Proinflammatory cytokines also induce HPA axis activity and β-endorphin release that affects the

central control of breathing, the sleep-wake cycle, the sensation of fatigue, and cerebral function (21). β-endorphins decrease respiratory muscle activation, resulting in more shallow, rapid breathing, possibly in an attempt to minimize further injury.

Dyspnea is closely related to anxiety. Sensory feedback from peripheral respiratory mechanoreceptors may contribute significantly to this respiratory sensation. During weaning from mechanical ventilation, respiratory effort may be perceived as being disproportionate to the breath achieved. This "neuroventilatory dissociation" is a disparity between expectation and reality and elicits psychological and neurohumoral responses, particularly anxiety and distress (20). Anxiety has several physiologic consequences. Higher respiratory rates increase respiratory work while the rise in muscle tone increases respiratory effort. Muscle deconditioning leads to discoordinated breathing, again increasing load. Circulating catecholamines rise, increasing ventricular afterload and cardiac work. Such patients are more likely to have significant intensive care unit complications, a requirement for longer-term ventilation and an increased likelihood of weaning failure with associated morbidity and mortality.

Selye's general adaptation syndrome

Many scientists have elaborated different models of stress. In 1936, Hans Selye described the paradox that physiologic systems that protect and restore the body can also cause harm (22). Stress turns into distress when the body can no longer withstand insults to which it is exposed, thus leading to functional compromise. He coined the concept of the "general adaptation syndrome" (22), a theory of stress involving numerous body systems with the purpose of maintaining equilibrium. When rats were injected with extracts from different body tissues, consistent changes were seen, regardless of the substance administered. These included swelling of the adrenal cortex, atrophy of the thymus, spleen, lymph nodes, and liver, and the development of gastric and duodenal ulceration. He also documented edema formation, accumulation of pleural and peritoneal transudate, loss of muscular tone, and falls in body temperature. He later showed that any acute nonspecific noxious insult, such as exposure to cold, surgical injury, spinal shock by cord transection, excessive muscular exercise, and administration of various pharmacologic agents could reproduce this syndrome (23). Indeed, Selye had just discovered the phenomenon of stress-related disease. Although inflammation and the immune response are essential for adaptation and short-term viability, they also carry long-term costs to health. Stress, defined by Selye, "is not a vague concept, somehow related to the decline in the influence of traditional codes of behavior, dissatisfaction with the world, or the rising cost of living, but rather that it is clearly a definable biological and medical phenomenon whose mechanisms can be objectively identified, and with which we can cope much better once we know how to handle it."

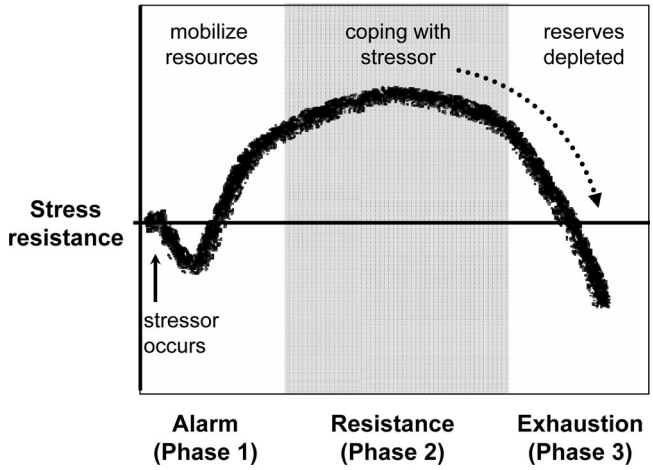

Figure 1. Selye's general adaption syndrome.

Stress is not a specific reaction to a specific insult. It can be produced by virtually any agent but is not necessarily undesirable. The stress of failure, humiliation, or infection is detrimental whereas that of exhilarating and creative work is beneficial. The stress reaction, like energy consumption, can be both good and bad. Selye's general adaption syndrome (23) defines an integrated syndrome of closely inter-related adaptive reactions to nonspecific stressors. He described three stages: the alarm reaction, the stage of resistance, and the stage of exhaustion (Fig. 1). After a period of time, the ability to resist the stressor would plateau and eventually decrease as the individual becomes fatigued. This third stage–the exhaustion/chronic exposure phase—is associated with increased morbidity and perhaps even death as the body becomes susceptible to tissue damage. Rather than the stress response running out, as Selye suggested through depletion of hormone stores, it appears that with sufficient activation the response may become more damaging than the stressor itself (24).

Allostasis and allostatic overload

The concept of "allostasis" was first coined by Sterling and Eyer in 1988 (25) and subsequently developed by McEwen (17, 18, 26) to describe both adaptive and maladaptive responses to stress. Whereas homeostasis, from the Greek *homeo*, "same" and *stasis* "stable" infers "remaining stable by staying the same," allostasis is derived from *allo* "variable" and *stasis* "stable" thus "remaining stable by being variable."

This allostatic model of actively maintaining stability through change suggests that the goal of regulation is not constancy, but rather an adaptability that constrains regulation to be efficient, thereby minimizing errors and optimizing performance at the least cost to the body. Through allostasis, the autonomic nervous system, HPA axis, and the cardiovascular, metabolic, and immune systems protect the body by responding to internal and external stresses. Allostasis thus distinguishes between systems essential for life (homeostasis) and those that allow the body to adjust to a new steady state in a changing, nonlife-threatening environment (allostasis). Thus, an unusual physiologic value should not necessarily be considered a failure to defend a set point. Sterling argues that variation, often in anticipation of demand, is a key point underlying regulation (27). Some variables, such as oxygen, glucose, temperature, and osmotic pressure, have to be

closely regulated as the human brain in particular can only tolerate relatively narrow ranges acutely. An insult driving any of these beyond their design limits can trigger positive feedback cascades that may be rapidly lethal. Any catastrophic departure from stability therefore mandates emergency treatment directed at correcting these low-level processes. However, this is not the usual threat to which organisms are exposed on a day-to-day basis. Sapolsky (28) offers a useful analogy of someone stranded in the desert who attempts to maintain normothermia (and thus regain temperature homeostasis) by increased sweating. To compensate for the increased fluid and salt losses from sweat, the kidney passes less urine in an attempt to prevent/minimize the decrease in circulating volume, the heart rate increases to maintain cardiac output, and so forth. Thus, heart rate and urine output have allostatically adjusted to the changing environment to optimize body functioning.

Allostasis thus allows the individual to respond to changes in his/her environment and to cope with challenges by both initiating a response and terminating it once the danger has passed. A stressor induces an allostatic load, leading to release of allostatic mediators such as cortisol and epinephrine. These promote adaptation and are generally beneficial whereas cumulative changes from a persistent or repetitive load—allostatic overload—can lead to wear and tear and possible pathophysiologic consequences. McEwen et al (26, 29) described four situations associated with allostatic load and overload: 1) Frequent exposure to stress due to repeated "hits" with multiple stressors; 2) failure to adapt (habituate) to repeated exposure to the same stressor; 3) inability to shut down allostatic responses promptly, and 4) inadequate response to stressors that trigger compensatory hyperactivity of other mechanisms.

Both body and brain have a huge capacity for adaptive plasticity. This may be either beneficial, minimizing future damage, or detrimental through increasing basal load. The ability to adjust to repeated stress is determined by how the situation is perceived; if viewed as a threat, then behavioral and physiologic responses will occur with inherent consequences.

This adaptive plasticity allows the body to meet loads that it will commonly meet and to retain a degree of reserve to cope with unusual loads. All body systems should therefore be optimally matched with each other; it would be inefficient for organs to provide excess capacity over and above that which could be used downstream, or for downstream organs to provide more capacity than they can be supplied with. However, this capacity should neither be overengineered to cope with unlikely loads, as this will be inefficient, nor be underdeveloped such that the body would disintegrate in response to regularly faced demands. Fluctuations around a set point thus occur in response to demand or in anticipation of demand. These will rise or fall in response to specific signals. Matching of need provides a far more efficient use of capacity and fuel utilization as the organism moves between markedly different states; crucially, it must retain the flexibility to do so. Effector systems change more slowly than sensor systems as this is more costly. A bout of intense exercise will make little difference to capacity, but only when repeated frequently (training) do alterations occur in muscle mass, mitochondrial number and activity, heart and lung capacity, cardiac output, and so forth, to adapt to this enhanced requirement. When the individual detrains, extra capacity is rapidly lost as the effector systems reconfigure back to the reduced need.

Allostatic Overload–Types 1 and 2. All organisms thus adjust their physiology and behavior in response to their environment. If stressors are unrelenting to such an extent that the HPA axis stops functioning as designed, those processes that were designed for short bursts become continuous and then start altering biology much sooner than originally intended. Changes in environment, food supply, or status can result in energy imbalance: type 1 allostatic overload–where demand for energy exceeds supply (29). The allostatic response aims to reduce this energy imbalance, promoting survival, and enhancing fitness. These rapid changes are collectively called the emergency life history stage and serve to direct the animal into a survival mode. Glucocorticoids and the HPA axis coordinate this response within minutes to hours (29). Type 1 overload is predominantly a protective mechanism, resulting in changes in behavior, sleep-wake cycle, feeding patterns, and so forth. However, these adaptations can also result in damaging changes to reproductive pattern, body condition, and survival. Importantly, the normal life cycle can be restored once the perturbation passes.

Type 2 allostatic overload, on the other hand, occurs when there is sufficient or even excess energy consumption. Secretion of corticosteroids and activity of other allostatic mediators (such as the autonomic nervous system, other neurotransmitters, and proinflammatory cytokines) rise and fall with allostatic load. If allostatic load remains chronically high, glucocorticoid levels remain high, appetite increases, insulin resistance can occur, and increased fat deposition ensues. The pressures of modern society appear to promote type 2 overload with coronary vascular disease, diabetes, obesity, psychiatric illness, etc. As type 2 allostatic overload does not trigger an escape or survival response, it can only be counteracted through learning and changes in behavior and social structure.

Why do different individuals cope differently with similar stressors?

Environmental conditions may differentially affect allostatic load in different individuals (8). Allostasis has shaped the course of evolution by allowing adaptation to the environment, food availability, season, social status, and environmental change. However, the cost of stress-induced adaptation is allostatic overload and stress-related disease. The Darwinian concept of stress describes adaptive strategies for coping with stress in a range of different organisms. Homogeneity within a group of organisms limits adaptation and is detrimental to survival, whereas variation allows competitive advantage in different situations. Indeed, different behavioral traits offer various advantages and disadvantages in terms of evolution and natural selection. Aggressive, proactive "hawks" employ fight-flight strategies that are confrontational in approach and tend to metabolize large amounts of energy. They are therefore more suited to high-density populations with abundant food sources. On the other hand, the cooperative, passive dove approaches situations with more caution, is reactive rather than proactive, and tends to have lower energy consumption. Doves are therefore at an advantage when population density is lower and food scarcer. Each behavioral type is therefore predisposed to different typical allostatic loads.

Some people are clearly more vulnerable to stress-related diseases than others. There are considerable individual differences in coping, based on interacting

genetic, developmental, and experiential factors. Genetic factors do not account for all individual variability in sensitivity to stress, as evidenced by disconcordance between identical twins (30). Early life experience may carry even greater weight in determining how an individual will react to a stressor. For example, early physical or sexual abuse can produce long-lasting emotional problems and changes in brain structure and function with an increased risk of depression, post-traumatic stress disorder, idiopathic pain disorders, substance abuse, and antisocial behavior (17). Conversely, a positive social support network and good self-esteem may have a positive influence on allostatic load.

How could allostatic overload relate to critical illness?

Although the precise pathophysiology underlying the development of multiple organ dysfunction/failure in critical illness still remains obscure, some important clues exist. It is clearly related to an exaggerated inflammatory response with excessive production of both pro- and anti-inflammatory mediators. This exaggeration is marked either in terms of response or duration. Likewise, catecholamine levels are massively elevated for prolonged periods of time; indeed, high levels maintained over time relate to poor prognosis (31). Significant activation of the HPA axis also occurs. Although focus in recent years has been focused on the depressed cortisol response to exogenous corticotrophin, Annane et al (32) also demonstrated that a high basal level of plasma cortisol was a strong indicator of subsequent mortality.

We have previously argued that multiorgan failure represents a hibernation-like response to a major insult whereby, in the face of prolonged inflammation, energy production and metabolism switch off as a later-stage adaptive strategy to maintain long-term organ viability should the patient survive (33). This hypothesis is supported by several findings, including histologic "normality" of failed organs (34), a preservation/increase in tissue oxygen levels (35), and the relatively unusual need for long-term organ support (36). An analogy can thus be made to allostasis and allostatic overload. An initial fall in organ perfusion after a severe cardiorespiratory insult results in early compensation as homeostatic and allostatic mechanisms kick in, the latter being coordinated by rapid changes in circulating glucocorticoids and catecholamines and in autonomic function. However, a severe and prolonged supply-demand energy imbalance will lead to a "type 1 allostatic overload." Unless there is rapid restoration of perfusion, the cell that maintains its normal functional processes will deplete its energy stores; once adenosine triphosphate levels drop below a critical threshold, cell death pathways are activated. In the absence of cellular resuscitation, the organ enters into a state of metabolic shutdown to preserve the failing fuel supply for processes vital for cell survival, and to place death pathways into abeyance (33). Although this will compromise normal cellular function and processes in the short-term, it offers the only viable solution to enable subsequent recovery.

An allostatic view of managing the critically ill patient

The homeostatic model of stability through constancy has dominated medical thinking and practice. So when a variable deviates from its set-point value, the emphasis of patient management has been primarily focused upon restoring the "inappropriate" value to "normal." However, treating these abnormal numbers with drugs and/or mechanical support devices to "fix" the disrupted—although not necessarily broken—low-level mechanism does not always bode well in the longer term. Intensivists have recognized over the last 10 to15 yrs that efforts to normalize physiology, e.g., through additional blood transfusion (37) or more aggressive mechanical ventilation (38), offer short-term fixes but more detriment in the medium- to long-term. We have thus learnt to become more permissive, be it through allowing acceptably abnormal levels of oxygen, carbon dioxide, hemoglobin, and blood pressure, preventing "over" feeding (in essence, normal feeding), and so forth.

Sterling identified three problems with targeting low-level mechanisms (27). First, as each signal triggers a cascade of effects, even the most specific molecular antagonist or inhibitor will have a widespread impact with possibly potent iatrogenic consequences. Second, the variables being targeted are also being driven to their particular levels by concerted signals from the brain, often in response to predicted or actual needs. Consequent suppression of one signal by a drug could lead to the brain driving other signals harder. Sterling cites the example of blood pressure control with a diuretic reducing circulating volume but driving compensatory tachycardia and vascular tone. Third, clamping to a target level renders that particular variable insensitive to predicted need and diminishes the ability for intrinsic modulation; this clamping thus opposes the whole purpose of physiologic regulation with a consequent impact on performance. For example, β-blockade will keep blood pressure low but often at the cost of exercise intolerance with the heart being less able to increase cardiac output when needed.

Numerous exemplars exist in critical illness management to highlight the consequences of (over-)correction, or interfering with one system without paying due regard to the impact on others. For instance, catecholamines are used to drive blood pressure up to an often arbitrary level, notwithstanding the normal natural variation in blood pressure that often falls markedly during sleep. This extrinsic "stress" results in a multitude of covert problems comparable to those described earlier with prolonged overproduction of intrinsic catecholamines. These include decreased cardiac efficiency and failure, immunosuppression, muscle breakdown, thrombogenicity, insulin resistance and hyperlipidemia, and metabolic inefficiency (39). Likewise, our rather indiscriminate use of proton pump inhibitors, despite a startling lack of evidence, will compromise both neutrophil bactericidal activity (40) and the gastric acid barrier, predisposing the patient to secondary infections including *Clostridium difficile* (41) and, in cirrhotics, spontaneous bacterial peritonitis (42). Another example is the attempt to drive enteral nutrition when the gut is delivering strong signals that this is unwelcome, e.g., through large gastric aspirates or abdominal distension. We may thus be interfering inappropriately with the allostatic responses that divert blood flow away from the gut to other more crucial areas and increase the hormonal output that suppresses appetite while boosting the immune response (43, 44).

The allostasis model argues for different therapeutic goals. If the brain regulates both physiology and its supporting behavior, then treatments directed just at the peripheral physiology may be countered by changes in behavior. So, rather than simply using drugs to hit low-level targets such as blood pressure, it may be more advantageous to focus instead upon

the physical and psychological disruption that accompanies critical illness. Our bodies have not evolved to cope with modern-day management of critical illness. From a teleological point of view, the acute stress response is intended to be a short-term "blast," self-terminating within hours to a few days at most, rather than a prolonged condition lasting weeks or even longer. Should we thus address more aggressively higher-level signals that stimulate both physiology and behavior? Sterling defines health allostatically as optimal predictive fluctuation (27). When the probability of demand shifts in either direction, so should the response (Fig. 2). The system becomes unhealthy when effectors adapt so forcefully during prolonged periods of high demand that they cease to reverse promptly when the prediction reverses. Although drugs and mechanical supports can force the response back to its original level, the response sensitivity is altered. Decreasing pressor responsiveness (vascular hyporeactivity) to prolonged catecholamine infusion exemplifies this point. Perhaps a more rational therapeutic goal would be to alter the predicted distribution of demand back toward its original level. Effectors can thus naturally re-establish their flexible variation around the predicted lower demand, thereby preserving the range of responsiveness. "Adaptation" in this sense refers to a resetting of response sensitivity. Although this may turn out badly, the outcome is not caused by any low-level defect and should not therefore be necessarily tagged as inappropriate or dysregulatory. This generates an interesting dilemma in that the patient may still die yet with their internal regulatory mechanisms remaining intact.

The challenge therefore is to better understand how the body responds to critical illness and how these are modulated—positively or negatively—by our management. In the interim we can perform simple and straightforward maneuvers that can destress the patient including facilitating sleep and restoring circadian rhythms (45–47), decreasing noise levels, (48) avoiding pain and discomfort, and providing anxiolysis. Sleep disturbance, for example, is a well-recognized allostatic load (49). It affects blood pressure, decreases parasympathetic tone, increases proinflammatory cytokine and cortisol levels, oxidative stress markers, and brain glycogen levels. These can impair axonal function and decrease psychometric performance. Cognitive impairment occurs in noncritically ill patients even with a modest sleep restriction of 6 hrs (49). Sleep deprivation is also associated with behavioral change, irritability, and aggression, all features of delirium now increasingly recognized in the intensive care unit patient (45).

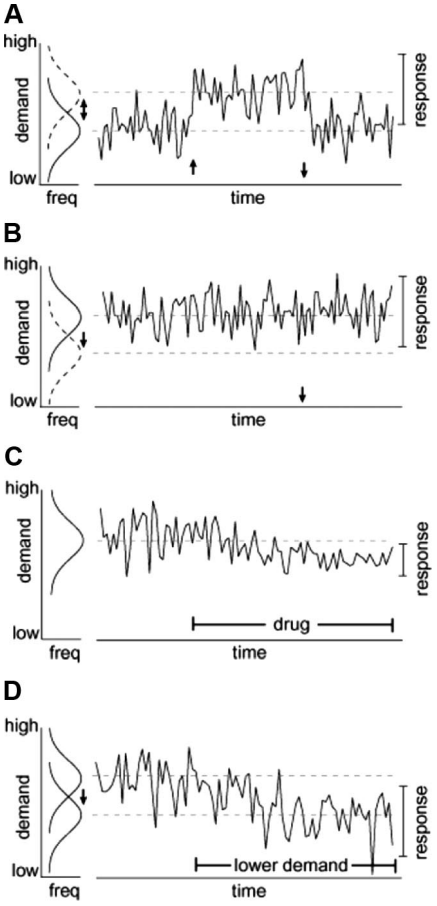

Figure 2. Where to intervene? (*A*) Healthy system. As demand distribution shifts upward briefly, the response distribution follows to maintain variation centered on most probable demand. As demand distribution returns to its initial state, the response distribution follows. (*B*) Unhealthy system. When high demand predominates for a long time, the system adapts to this expectation. When demand is reduced briefly, the system does not return to the initial state. (*C*) Standard pharmacotherapy. While demand stays high, drugs that antagonize key effector mechanisms force the response distribution back toward its initial mean. However, this reduces responsiveness and evokes iatrogenic effects. This should be expected because the organism must continue to meet elevated demand but with fewer or weaker effectors. (*D*) Rational therapy. When demand is reduced for long periods, the system re-adapts to the initial demand distribution. The mean response returns to its initial level while responsiveness is maintained. Reproduced with permission from Sterling (27).

In addition to the above, sympathetic overstimulation can also be prevented by avoiding tissue hypoperfusion, averting muscle deconditioning by early mobilization and regular exercise, and by not overfatiguing during excessively rapid or prolonged weaning from mechanical ventilation. More provocatively, β-blockade could be selectively used. This has been shown to be relatively safe in an uncontrolled series of septic shock patients (50) and to benefit children after burn injury in reducing their degree of catabolism and loss of muscle mass (7). Other potential antistress agents are angiotensin II receptor blockers such as candesartan (51). Arguably, long-term sequelae of critical illness including neuropsychiatric problems (depression, posttraumatic stress disorder, hallucinations, etc.) and decreased mobility will also be ameliorated by antistress approaches.

CONCLUSION

Stress is an integral part of the body's defense against extrinsic (or intrinsic) insults. A failure to mount an adequate stress response is clearly associated with worse outcomes. Thus, whereas some stress is both appropriate and protective in the short-term, excessive and/or prolonged stress compromises the body's allostatic responses, leading to pathology. An increasing awareness and acceptance of this concept should encourage further efforts to minimize stress in the critically ill patient by reducing demand through both specific and general measures and accepting abnormal physiologic levels that are still compatible with survival.

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