



Stress dysfunctions as a unifying paradigm for illness: Repairing relationships instead of individuals as a new gateway for medicine

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Summary Stress has been implicated as a risk factor for most diseases, but a mechanistic explanation behind such associations remains elusive. As emergent responses to stress, adaptations range from acute responses where extant system capabilities mitigate current stress, to longer-term responses where system plasticity buffers against future stress. The long compendium of human ailments manifests through a much shorter set of symptoms that may operate through the stress axis. We propose a unifying ontology for human illnesses that classifies stress dysfunctions according to types of Darwinian dysfunction – inadequate response with adequate adaptation, inadequate adaptation, inappropriate adaptation, and epiphenomena of adaptation. Examples include cancer as a bystander effect of increased biologic plasticity in response to stress, and infectious illness as a manifestation of mutually escalating stress in an otherwise commensal relationship between hosts and microbes. We explore the contributing role of man-made stresses that have emerged as humans increasingly remodel their environment. Examples include biologic decompensation associated with reliance on technology to buffer stress, and behavioral stress caused by the dislocation of kin networks that promotes illegitimate signaling. Dysfunctional relationships engender stress not only among humans, but also among individual organs; heart failure, renal failure, and carotid stenosis may represent examples of such conditions. If stress dysfunction is the Occam's razor of human illnesses, and derangements in biologic relationships induce stress dysfunctions, then the study of relationships – an incarnation of systems biology – may represent a new gateway for medicine.

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Hypothesis

Stress has been anecdotally or empirically implicated as a risk factor in virtually all human ailments including cardiovascular diseases, infection,

inflammation, gastrointestinal conditions, pulmonary diseases, autoimmune diseases, genitourinary conditions, infertility, dermatologic diseases, neuropsychiatric conditions, and cancer [1–4]. However, a mechanistic explanation for these associations remains elusive.

John von Neumann, Stephen Wolfram, and others have demonstrated that apparent complexity can arise from very simple core principles [5]. We

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believe that this theory can be applied to deciphering the link between stress and human illnesses. Although the catalog of named diseases is long, we note that a much shorter list of symptoms characterize all of human illness. Interestingly, stress pathways such as autonomic dysfunction participate mechanistically in every symptom surveyed during the “review of systems” [6]. In this paper, we hypothesize that stress dysfunction related to various types of Darwinian dysfunctions is the Occam’s razor of the compendium of human illnesses – the single explanation that answers many questions which initially appear unrelated.

Stress as a driver of adaptation

Fundamentally, stress (S) can be viewed as a state when the energy demands (E_d) on a system exceed the extant energy supply (E_s , such that $S = E_d - E_s > 0$). A stress response is the thermodynamic reaction of a system to those conditions. Consider a metal bar as it bends. When the energy demanded by the external bending forces exceeds the energy supply of the molecular bonds within the lattice structure, the system capitulates – the metal bar bends until the energy demand on the system falls below the level of its energy supply. Adding heat energy mitigates the stress and increases the probability of bending rather than breaking. Not surprisingly, in physics and engineering, stress is measured in terms of energy.

Biologic evolution can be characterized as an optimization of energy efficiency [7]; thus, we assert that biologic stress can be considered under a similar thermodynamic framework. Sources of stress for biologic systems can be classified into two categories: competitive and non-competitive. Examples of competitive stress are predation and infection, which represent threats to extant energy supply by predators or pathogens and demands for energy as fight-or-flight instincts activate. Examples of non-competitive stress include environmental resource depletion, which decreases access to energy supply, and falling temperatures, as maintenance of thermal homeostasis can increase energy demands.

In contrast to a metal bar, biologic systems emerge with reproducible and accruable adaptations to stress. Adaptations are emergent stress responses that span the temporal spectrum, ranging from acute responses that mitigate current stress based on extant system capabilities to longer-term responses enabled by system plasticity that buffers against future stress. Muscle exertion and production of IgM antibody are examples of acute stress

responses (energy expenditures) to a current energy demand, whereas muscle hypertrophy and production of IgG antibody are examples of long-term stress responses that reallocate existing energy resources in anticipation of future demands, i.e., a buffer. A buffer (B) can thus be described as a state of adaptation when the energy supply (E_s) exceeds the energy demand (E_d , such that $B = E_s - E_d > 0$). In the broadest sense, fitness represents the net summation of available buffers and attendant stresses. Evolution traces the fitness optimization that occurs when serial exposure to stresses drives the accumulation of thermodynamically efficient buffers which rely on energy assets – biomaterials and their relationships – to defray stress.

The stress minimum is a dynamic state since the environment constantly changes, bringing new energy demands and new opportunities for energy supply. As ongoing adaptations optimize fitness, reproductive isolation enables speciation and the occupation of new niches, characterized by more favorable circumstances of energy supply and demand. This biologic diversity buffers the ecosystem against the potential stress of future environmental displacements.

The discussion of concepts such as stress, buffer, and fitness requires awareness of the frame of reference with respect to region of interest or epoch of time. For instance, a system can exhibit high fitness for a particular duration, but low fitness over a longer period of time. While practical description requires defining a particular frame of reference, in nature the state of the system reflects the state of all regions of interest in the space–time continuum.

A metal bar breaks if a stress overwhelms the capacity of the lattice structure to exhibit thermodynamic plasticity – to adapt its thermodynamic organization and buffer the stress. Similarly, the plasticity of biologic stress responses also represents a function of time and capabilities. Environmental change may overpower the constraints of available biologic design, and change may also occur over a time scale inconsistent with phenotype and genotype plasticity. If a particular system accumulates sufficient levels of stress dysfunctions, illness or death may ensue. The death of sufficiently stressed individuals through programmed self-termination, a process known as phenoptosis, may paradoxically enhance inclusive fitness [8].

Illnesses as stress dysfunctions

Based on these concepts, we propose the following ontogeny which reclassifies human disease into four

broad categories of stress dysfunctions according to the type of Darwinian dysfunction involved. (1) Illness can arise when a biologic system encounters a stress beyond its capacity for acute response. Bone fracture is a classic example. However, if the biologic plasticity of the system enables sufficient adaptation, the illness then abates, as when a fracture heals. (2) If the stress extends beyond both the acute response capabilities as well as the long-range biologic plasticity, then a chronic ailment can ensue due to failure of adaptation. An example is a fracture that fails to heal. (3) Chronic illness can occur when Darwinian dislocations, as defined in the section that follows, induce extant stress responses to behave in a harmful way. (4) Chronic illness can also occur as epiphenomena of the activation of biologic plasticity during stress. The last two categories are discussed further.

Stress dysfunctions that represent darwinian dislocations

Changing conditions can render existing buffers to behave in a maladaptive fashion, a phenomenon we term “Darwinian dislocation”. For instance, the legacy stress response during periods of stress is caloric hoarding, which was likely adaptive during the prehistoric era, when nutritional stress related to resource scarcity was presumably more common [9]. In the modern era when human stress responses are maladaptively triggered despite caloric abundance, caloric hoarding contributes to obesity.

In some cases, stress dysfunctions may even set up iterative exacerbations of an ailment. Consider the example of hypertension associated with carotid stenosis. Such patients are predominantly treated with drugs that target blood pressure, yet hypertension and carotid stenosis often insidiously progress even while the patient receives therapy. A carotid plaque may render dysfunctional the relationship between signal (intraluminal pressure) and sensor (carotid baroreceptor). The carotid baroreceptor may under-report intraluminal pressure and may raise systemic sympathetic tone in a maladaptive effort to increase blood pressure. In turn, the higher sympathetic tone may exacerbate the carotid plaque burden [11], which may further the dysfunctional relationship between blood pressure and carotid baroreceptor, setting up a nefarious feed-forward cycle. Other examples include the feed-forward cycles of acute coronary syndromes, stroke, congestive heart failure [10], and renal artery stenosis [12]. In these conditions, individual organs or physiologic systems may generate functional responses, but because the relationships

between the responses have become dysfunctional due to Darwinian dislocations, unintended negative consequences may still arise.

Illnesses as epiphenomena of stress response

Severe levels of stress can induce living systems to rely on riskier methods for generating compensatory adaptation, not unlike how the proverbial cornered mouse behaves under extreme duress. Examples of riskier methods of adaptation include increasing the genotypic and phenotypic variation through specific and nonspecific mechanisms such as heat shock proteins [13], relaxation of the error proofing during DNA replication [14–16], reduced stringency of chromatin-mediated gene repression, and RNA-based silencing. While the biologic plasticity afforded by each of these measures can engender creative adaptations to contend with stress, the reduced fidelity to the status quo carries a stochastic risk of a deleterious outcome. Illnesses can arise as epiphenomena of such increased biologic plasticity in response to stress.

Cancer may exemplify this process [17,18]. Repeated traumatic or infection-related stress is known to produce squamous cell carcinomas [19,20]. Other examples include cervical cancer (human papillomavirus) and Burkitt’s lymphoma (Epstein-Barr virus). Cancer can arise as a bystander effect of growth factor or stem cell recruitment to stressed tissues [21,22]. Copper deficiency, a resource stress [23], can manifest in a leukemia-like phenotype which reverses when the resource is replenished [24]. Similarly, congenital forms of leukemia associated with the stress of childbirth spontaneously regress after the stress wanes [25]. Even the conventional wisdom that environmental carcinogens and radiation can cause cancer through direct genomic alterations may need refinement. Perhaps some neoplastic phenotypes arise due to a bystander effect while searching for genomic innovations to contend with the oxidative and cellular stress associated with exposure to radiation and carcinogens. The bystander effect may represent the second hit of the Knudson two-hit hypothesis of oncogenesis. This mechanism may explain recent studies which have shown that exercise, an activity which promotes stress reduction, can retard the carcinogenic effects of ultraviolet radiation [26]. Similar bystander effects may underlie a wide range of conditions associated with stress that involve derangements of phenotype and genotype plasticity, such as autoimmune dysfunctions, degenerative conditions, and protein misfolding.

The stress dysfunction hypothesis suggests a novel theory for the pathogenesis of infection. A

widely held notion presumes the baseline *modus operandi* of microbes to be the exertion of hegemony over hosts through invasion, with impaired host immunity associated with stress facilitating microbial expansion. We contend instead that microbes are no different than other organisms, and stress minimization comprises their fundamental imperative as well. The host represents a rich energy source, but also poses a predatory threat to microbes, and managing this balance represents a key element of the microbe–host relationship. We assert that most known and countless undocumented microbes seek and enjoy a commensal relationship with their hosts. Notably, the same agents purported to cause diseases such as strep throat (*Streptococcus pyogenes*), gastrointestinal ulcers (*Helicobacter pylori*), meningitis (*Neisseria meningitidis*), and pneumonia (*Staphylococcus aureus*) can be cultured from asymptomatic patients, suggesting that without stress dysfunction, microbial presence alone may not necessarily produce illness. Zoster is among the many illnesses that arise when acute stress causes an existing infectious agent to convert from dormant to aggressive. The association of gastrointestinal ulcers with both stress and *H. pylori* also supports the notion that the relationship between host and microbe, and not merely the presence of the microbe itself, determines the potential for pathogenesis.

The experience of infectious illness may arise when stress introduced into the host–microbe relationships by either party induces behavioral change in the otherwise benign counterparty. Since the ability to detect and respond to stress in counterparts can confer fitness advantages, many organisms, including microbes, may have evolved such abilities. For example, as an aspect of quorum sensing, microbes possess adrenergic receptors which enable the ability to respond to host stress signals such as catecholamines [27] and presumably cortisol, vasopressin, aldosterone, and renin as well. If stressed by external factors or resource scarcity, a microbe may induce stress in the host–microbe relationship by aggressively attacking the host to resolve its own stress. On the other hand, if the host introduces stress into the microbe–host relationship, the previously unstressed microbe may seek to mitigate its own stress by altering its genotype and phenotype. The microbe may (1) counterattack by invoking behaviors that in turn may activate host stress responses, leading to an escalating exchange of induced stresses and responses – a fractal equivalent of the mutual provocation frequently seen in war; (2) enter a dormant state; or (3) seek escape routes to other hosts. The first type of response may underlie the

experience of illness, while the third type of response may enable contagious dissemination. When stressed microbes establish beachheads in new hosts, the agitated state of arriving microbes may induce host stress responses and provoke the aforementioned cycle of mutual stress escalation.

Our hypothesis may help explain why physiologic and behavioral stressors can trigger infectious illness. The arrival of winter brings thermogenic demands which activate sympathetic bias, a state of stress [28]. Childhood and old age are periods in life characterized by sympathetic bias [28]. The common locations for infections include those sites that manifest relatively high functional sympathetic bias, such as distal extremities and mucosal surfaces [29]. Airplane flights are associated with stresses related to acute hypobaric hypoxia, acute thermal demands, and psychological fear [30]. All of these triggers of stress are also anecdotally associated with an increased risk of infection – an association commonly blamed on the putative immunosuppressive effects of stress. Perhaps these and other everyday sources of physical or psychological stress activate host stress responses, which may force otherwise neutral microbes to activate their own stress responses in mutually escalating fashion to produce illness. In some cases, the host stress response may generate diseases as epiphenomena to microbial proliferation, such as in the case of glomerulonephritis with *Streptococcus pyogenes* and *S. sepsis*. Immunocompromised states such as HIV infection, chemotherapy, and chronic steroid exposure may promote infectious illness due to their augmentation of host stress. Paradoxically, acute steroid production comprises the mechanism by which the body quells its own stress response. Not surprisingly, acute steroid administration appears to be beneficial in certain infections and may warrant studies in others [31,32].

Man-made stress

Cognition is one of the most powerful adaptations to emerge during evolution. While remodeling the environment to buffer against stress is nothing new in natural history – birds building a nest, for example – cognition has enabled humans to do so to a profound extent. Although environmental remodeling confers immediate benefits of stress reduction, human interventions often produce unintended, undesirable secondary stresses that may be just as profound. These modern phenomena may contribute to the broad rise of background stress in the population that could help explain the rising incidence of many chronic diseases [4].

Proximate benefit, ultimate harm

As stress drives adaptation, environmental stress can beneficially remodel biologic buffers in living systems. By following their instinctive proximate urges, however, modern humans are increasingly remodeling their environment rather than allowing the environment to remodel their bodies. While doing so reduces exposure to stressors that had been common to human predecessors, a stress experience that is too narrow or discontinuous can undermine the ability to buffer future stress [30,33]. Air conditioning and sun protection strategies may reduce acute stress, but weaken the body's ability to buffer future thermal and radiation stresses [30,33,34]. Ergonomic solutions may reduce short-term energy demands on humans, but the resulting biologic complacency and sedentary lifestyles afforded by modern conveniences can induce cardiovascular deconditioning, decreased heart rate variability, increased autonomic dysfunction, and multiple associated sequelae [10].

The rise of modern farming techniques has transformed the relationship between humans and their energy and nutritional supply. On one hand, the previous scarcity and volatility of resource supply have decreased, thereby reducing the stress associated with food acquisition. On the other hand, as extant preferences for salt, sugar, calories, and fat become decoupled from their previous environmental scarcity, many food-related health dysfunctions such as Syndrome X arise. Furthermore, unnatural farming conditions that favor business efficiency may promote food chain stress, assimilated by the unwitting consumer in a phenomenon known as xenohormesis [9].

Illegitimate signaling and behavioral stress response

What the popular literature commonly calls "stress" is the behavioral experience of a stress response to a perceived stress. One might surmise that the behavioral stress response represents an adaptation that modifies behavior to buffer against future stress. For instance, depression that results from chronic underexposure to sunlight may have evolved to drive the individual away from existing conditions and towards a potentially more favorable energy environment. However, we believe that the behavioral stress response is often rendered maladaptive today due to Darwinian dislocations.

Modern behavioral responses to social cues such as fear, envy, and trust were predominantly pro-

grammed during a evolutionary epoch dominated by kin networks that optimized inclusive fitness [35]. However, modern transportation and communication technologies have largely dissolved such kin networks, and humans are increasingly interacting with non-kin. The degree of Darwinian dislocation of social structures can exceed the programmed plasticity of social responses forged during the kin-network era. As a result, we are witnessing the rise of illegitimate signaling that exploits legacy behavioral cues such as advertising, spam, pornography, and media distortions.

Behavioral exploitation for the purposes of fitness transfer may generate audience stress. Advertising can instill a sense of inadequacy and discontent. Media news often focuses on negative events, pandering to a pre-existing adaptation that drew audience attention to vignettes of evolutionary value such as sex and violence – something we term "Darwinian rubbernecking". The social behavior of increasingly disconnected communities has become characterized by fear, distrust, concerns about crime, diminished altruism, information overload, and a decline in the overall quality of relationships [6,36], all of which can induce the behavioral stress response. These examples are among the many social dysfunctions that render the behavioral stress response maladaptive given the dislocation from its intended use. Whereas the prehistoric human era has been described as one of good psychiatric health [37], illegitimate signaling in the modern era has contributed to the increasing prevalence of psychiatric dysfunction. As the food chain example cited in the previous section demonstrates, illegitimate signaling can impair the relationships of humans not only with each other, but also with their food chain and their ecosystem [9].

Modern medicine as an example of man-made stress

The modern medical paradigm generally entails a correction of errors – replace what is deficient and block what is in excess. In essence, modern medicine attempts to compensate externally for internal buffer insufficiency. For example, if the body fails to normalize an upward deviation of blood pressure, a physician might prescribe a drug that compensates. However, this well-intended therapeutic strategy to solve a proximate problem may ultimately worsen the underlying dysfunction in paradoxical fashion [38]. Whereas the stress experience may be necessary to strengthen underlying buffers – this may explain why raising blood

pressure and heart rate during exercise lowers the background rates of both parameters – modern therapy often undermines those buffers by acting as a crutch.

The placebo effect hints at the benefits potentially realized in virtually all major disease classes by reducing stress in the relationship between patients and the medical community. The practice of medicine – that is, the physician–patient encounter and the many stressful rituals traditionally associated with this interaction – may require reconsideration once the relationship between stress dysfunctions and disease becomes better understood. Prolonged waiting room time, “white-coat” effect, fear of needles, procedure anxiety, poor communication, and the physical stress of invasive procedures are among the many sensory experiences associated with doctors’ visits and hospitalization that comprise potential sources of patient stress – a phenomenon we term the “anti-placebo” effect. Furthermore, the stressful methods used to train young physicians may promote unhealthy lifestyles, and may make it difficult for doctors to become social role models for stress management.

Perspectives

Medicine reconsidered

If stress dysfunction is the fundamental cause of disease, what are the new opportunities to benefit patients? To better define the opportunity, consider the extant model of medicine, which is currently biased towards individualism. Generally speaking, physicians treat individual patients; specialties are organized around individual organs; and scientists study individual genes. Therapy predominantly targets a downstream symptom rather than an upstream inciting stress. Even when stress is addressed at the patient level, the patient is often treated pharmaceutically as an isolated individual.

However, stress is ultimately a function of the impaired relationship between an individual system and its environment. In this paper, we demonstrated how diseases may arise from the physiologic stress of dysfunctional relationships between organ systems and the behavioral stress of dysfunctional relationships in the concentric layers of context in which they live – their families, their communities, and their world. On the other hand, it is apparent that sound relationships can serve as effective buffers against stress. Recent theoretical modeling work presented by Dr. Francisco Jose Ayala suggests that if proper thermody-

amic relationships are in place, the number of integrated units in a system needed to sustain robust buffers against stress can be astonishingly small (personal communication). Despite the seductive undertow of reductionism and individualism, we propose that a shift in medical sciences towards the study of biologic relationships could yield new insights into solutions for human ailments.

Many potential applications are evident. In the previously mentioned case of hypertension associated with carotid stenosis, even when the carotid baroreceptor and the blood pressure regulation systems may individually be functional, the dysfunctional relationships between the individual systems can engender disease. Using atherectomy to restore the normal relationship between intraluminal blood pressure and carotid baroreceptor perception may prove beneficial. In the case of obesity, the behavioral stress response and the caloric hoarding response during stress may each be functional unto themselves, but once again the relationship between the two responses may be dysfunctional. If the patient merely reduces caloric intake without reducing behavioral stress, the body may misinterpret caloric decline and further escalate caloric hoarding tendencies. Reducing behavioral stress in addition to nutritional stress may prove more beneficial.

Given the prevalence of illegitimate signaling, normalizing family, vocational, and community relationships may benefit health. Normalizing ecological relationships may also reduce the stress experience in the food chain and thereby lessen the stress signals that humans consume through xenohormesis. Judicious expansion of the dynamic range of biologic stress experiences may restore the natural relationships between the body and the environment. Examples might include widening the range of exposure to temperature, sunlight, and optical focal length variation. In doing so, the buffers of the body may be strengthened rather than undermined by modern conveniences.

On the pharmaceutical front, drugs may be similarly employed to strengthen rather than to decompensate the natural buffers of the body when used for paradoxical indications [38]. In addition, we envision a potentially broader role for the local administration of steroids–hormones that mediate stress responses. We also anticipate the emergence of therapeutic approaches akin to adrenalectomy, sympathectomy, and neuromodulation that employ selective or global modulation of stress response pathways such as the hypothalamic–pituitary–adrenal axis and the autonomic nervous system. Similarly, new opportunities to

improve science and drug discovery may come from recognizing the influence that stress conditions may have on the phenotype of in vitro and animal model systems as well as biotechnology drug expression systems.

Evolution reconsidered

In our model, we have essentially characterized stress as a state of net energy demand and buffer as a state of net energy supply for any given system. Given the law of conservation of energy, the cumulative total stresses ($S = E_d - E_s > 0$) and buffers ($B = E_s - E_d > 0$) in a system sums to zero. Thus, in the total system, a change in the amount of stress is always accompanied by an equal counterbalancing change in the amount of buffers, and vice versa. The accumulation of buffers in one part of a system necessarily increases stress elsewhere in the system. This idea offers a potential framework to explain many intuitive observations. The apparent success of humans through the accumulation of buffers may come at the cost of counterbalancing stresses in the greater ecosystem. Human remodeling of the environment may lead to deforestation and loss of biodiversity. Ecologic and social diversity buffers the larger system from cataclysmic changes, but increases the competitive stress amongst the participants. On the other hand, the actualization of the global melting pot through modern transportation and communication may defray the stress of ethnic strife through mechanisms such as intermarriage, but such genetic convergence would also de-buffer the human species from cataclysmic environmental change. The concentration of wealth by individuals can be construed as an accumulation of buffers against future stresses. History has shown that the concentration of wealth by select individuals within a group can induce stress in the greater system as economic relationships strain. If sufficient stress accumulates, the wealth disparity is sometimes depolarized through a cataclysmic social upheaval.

Natural history suggests that living systems, themselves comprising accumulations of buffers, tend to preferentially accrue more buffers. This trend in turn would lead to a corresponding increase in stresses in the surrounding environment, suggesting that the current evolutionary trajectory constitutes a polarization of buffers and stresses. However, given our brief duration of existence, our view of history as a linear progression may simply reflect our limited vista on the proceedings. On a grand scale, perhaps history describes an indefinite wave function of polarization and depolarization, of stress and buffer. The inflationary phase

of the universe can be interpreted as the de-polarization phase of buffers and stresses. The deflationary phase of the universe can be interpreted as the polarization of stresses and buffers. Evolution may have begun as a response to the stochastic variation of energy through the universe. The perspective of stress and buffer as counterbalancing forces rationalizes the notion of duality in nature and in philosophy, of action and reaction, of yin and yang.

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