

# Systems Biology and the Stress Response: From Pythagoras and the Epicureans to Modern Medicine

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## Summary

“Stress” is defined as the disturbance in the “dynamic balance” or “homeostasis” of a complex system, such as the human organism or society, “stressors” as the forces that produce this disturbance, and “adaptive response” as the forces from within the complex system that strive to return homeostasis to normal. In the case of the human organism, the adaptive response is subserved by a specialized system in our brain and body, the “Stress System”, which is activated to help us deal with stress when a stressor of any kind exceeds a certain threshold. In itself, stress that is dealt with efficiently by the adaptive response of a complex system is neutral or even potentially beneficial to that system, be that an organism or a society. In contrast, the chronic dynamic state in which the adaptive response fails to fully reestablish homeostasis during stress, which I call “dyshomeostasis” or, more correctly, “cacostasis”, may have detrimental effects on the system. In human beings, the crucial beneficial hormones that are activated to reestablish homeostasis, the “homeostatic or stress mediators”, including adrenaline, noradrenaline, cortisol and the inflammatory mediator interleukin-6, are also, paradoxically, responsible to a great extent for the damage the organism sustains when in cacostasis. These mediators may impair the physiology of our cells, disturb their metabolic activity, increase their inflammatory response and stimulate their oxidative functions, all potentially damaging changes, ultimately accelerating aging, causing obesity, metabolic problems and osteoporosis, promoting atherosclerosis and cardiovascular disease and increasing the chance of the organism to be infected or get cancer.

The pre-Socratic philosophers Pythagoras and Alcmaeon, respectively, used the terms “*harmony*” and “*isonomia*” to express the dynamic balance or homeostasis of life, while the Hippocratics equated this harmony with health and disharmony with disease. Both the Stoics and the Epicurians, philosophic schools that concentrated on the study of stress and its management, considered the attainment of “*ataraxia*”, or imperturbability of the mind to stressors, as the ultimate goal of life, while Epicurus himself spoke of “*eustatheia*” -or “*eustasis*”, if we extrapolate from homeostasis-, the serene emotional state of a harmonious balance in a human being. The not uncommon Greek first name “*Eustathios*” is a remnant of that era. Based on these ancient seminal ideas, we suggested that appropriate responsiveness of the human stress system to stressors is a crucial prerequisite for a sense of wellbeing, adequate performance of tasks, and positive social interactions, and hence for the survival of the self and the species. By contrast, inappropriate, over- or under-responsiveness of the stress system through its hormonal and inflammatory mediators may impair growth and development, and may account for the many chronic behavioral, endocrine, metabolic, and allergic/autoimmune disorders that plague contemporary humanity. The development and severity of these conditions primarily depend on the genetic and epigenetic vulnerability of the individual, the exposure to adverse environmental- including psychosocial and socio-economic- factors and the timing and duration of the stressful event(s).

Our first model disorders of stress system over- and under-responsiveness were, respectively, melancholic depression, which we showed to be a disease characterized by chronic hyperactivation of the stress system, explaining its behavioral and somatic manifestations, and its mirror image, atypical depression, characterized by chronically decreased activation of this system, also explaining its clinical manifestations through a similar but alternative pathway. This realization allowed us to extrapolate our thoughts to the larger nosology of the human population, identifying many other such states. Starting from animal models, and with some surprise, we realized that hyporesponsivity of the stress system to inflammatory signals and resistance of immune tissues to cortisol characterize several inflammatory disorders, such as rheumatoid arthritis and septic shock, phenomena that we elucidated at the molecular level. Similarly, we identified other human

states characterized by hypoactivity of the stress response, including seasonal depression, the chronic fatigue and fibromyalgia syndromes, postpartum blues/depression and the late luteal phase dysphoric syndrome disorder.

We suggested that the genetic vulnerabilities of our species leading to the contemporary “chronic non-communicable diseases”, which include obesity, the chronic pain and fatigue syndromes, depression, hypertension, the metabolic syndrome and cardiovascular diseases, resulted from selective pressures of evolutionary stressors upon our genome during our evolution to modern human beings. To these genetic vulnerability changes, stress in prenatal and early life adds the so-called epigenetic ones. Prenatal life, infancy, childhood and adolescence are critical periods characterized by great plasticity and, hence, increased vulnerability to stressors. During these critical periods of life, stress mediators exert major organizational effects on the neural circuits of the brain and epigenetic effects throughout the brain and body. Such neural and epigenetic changes are environmentally acquired, and as such, are fully preventable.

Well beyond depression, currently affecting approximately 20% of the adult population and predicted by the World Health Organization to soon be the number 2 morbidity factor in the world, we suggested that chronic common, every day stress and the resultant cacostasis are also a major factor for all cause morbidity and mortality in today’s societies, encompassing all the chronic non-communicable diseases and, to a lesser extent, certain infections and cancer. At this time, and despite the stupendous advances in hygiene and medicine that have prolonged our lives, we believe that over 50 percent of the human disease burden is due to chronic socioeconomic distress, a result -to a great extent- of the ever increasing complexity and alienation in the modern world. We should note that the effects of prolonged distress go well beyond the causation of the chronic non-communicable diseases. Prolonged human cacostasis disturbs normal growth and development in children, causes emotional deprivation, upsets sleep, destroys family and social life, increases criminal behavior, multiplies violent accidents, and stimulates the abuse of and dependence on substances. Chronic distress also accelerates aging, reflected in decreasing chromosomal telomere length, and increases frailty, curtailing healthy life expectancy. Finally, the health care related costs of prolonged distress are enormous, probably accounting for a significant proportion of the total expenditures.

The dysphoria that most frequently accompanies cacostasis and the “happiness” of equanimity and sense of wellbeing are mutually inhibitory of each other. We now understand the neurochemical mechanisms of this crucial relation and can employ this knowledge in our quest for happiness and good health. We actually can, with the power of our will, lead ourselves to a dynamic state of homeostasis that is at a level higher than what would have been expected from our genetic and epigenetic constitution and our environment, a condition that I call “hyperstasis”. The latter state allows the full experience and appreciation of the gift of life, extends its duration and influences propitiously those around us. This state gives materialism its true proportions and promotes virtue, spirituality and a better Society.

Through our work, we established the common biological pathways connecting a large array of ostensibly disparate psychological and somatic disorders, including depression, anxiety, obesity, hypertension, metabolic syndrome, diabetes, allergic and autoimmune inflammatory disorders, sleep disturbances, such as insomnia and sleep apnea, hypofertility, and osteoporosis. We contributed to the understanding of how stress through its mediators, including components of the inflammatory reaction, causes premature aging, and promotes cardiovascular and neurovascular diseases. A common pathophysiology suggests that prevention and curative means have common bases.

Today, the presence of stress and cacostasis in an individual can be evaluated and graded. There are rational and proven methods to prevent and ameliorate distress that start from changes in lifestyle (healthy diet, exercise, stable daily timing, adequate sleep), to cognitive and behavioral therapies, to the use of appropriate medications. Indeed, the currently available medications that control risk factors and prolong life function primarily by blocking the stress system and inflammatory mediators. The key issue is that nature is not destiny and wellbeing and hyperstasis are attainable.

Granted that chronic distress in early life augments the risk of developing chronic behavioral and non-communicative disorders, preventing distress in pregnancy and the first 5 years of life or interrupting the vicious cycle of distress during this period is imperative and, in the long run, the most cost-effective

approach. Interventions beyond the age of 5 may be quite useful, but one should note that major stress-related brain organizational and epigenetic damage has already occurred. At this point I should mention what L. Tolstoy had intuitively said: *“From the child of five to myself is but a step. But from the newborn baby to the child of five is an appalling distance”*. Now, this is based on robust evidence and makes early interventions, starting with the education of prospective mothers, a must.

In summary, to interrupt the vicious effects of stress in a society and its members, one should, first, eliminate or at least moderate the stressors and, second, one should improve the coping of individuals with such stressors - aka improve their resilience to stress-. Political actions can influence both strategies: Granted that stress in today’s industrialized world is mostly anthropogenic, a well-run country itself in homeostasis, in which people feel enfranchised, dignified and dealt with fairness and justice, is bound to have happier and healthier citizens. On the other hand, preventing early life stressors and their effects on the very young will eliminate development of risks for the later behavioral and chronic non-communicable disorders that plague our societies today. Finally, like many human endeavors, coping with stress is an eminently learnable process and the basis of the most effective psychological therapy employed today, cognitive behavioral therapy. It is the duty of a Society to ensure the wellbeing and happiness of its people with political strategies that prevent stress and enhance the ability of its citizens to cope.