Medicina:

Esforço Comum da Promoção da Saúde e Prevenção e Tratamento das Doenças

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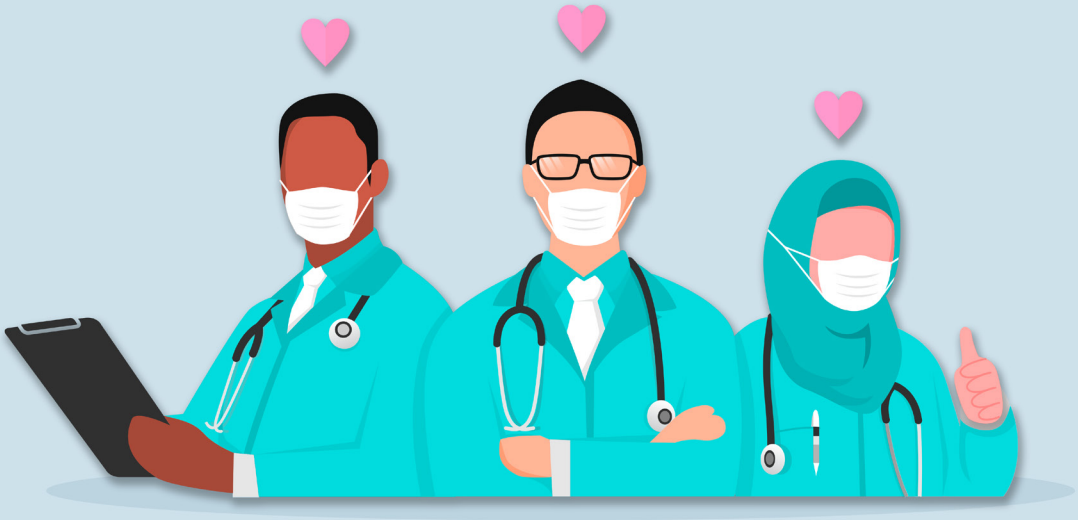

Benedito Rodrigues da Silva Neto
(Organizador)

Atena Editora
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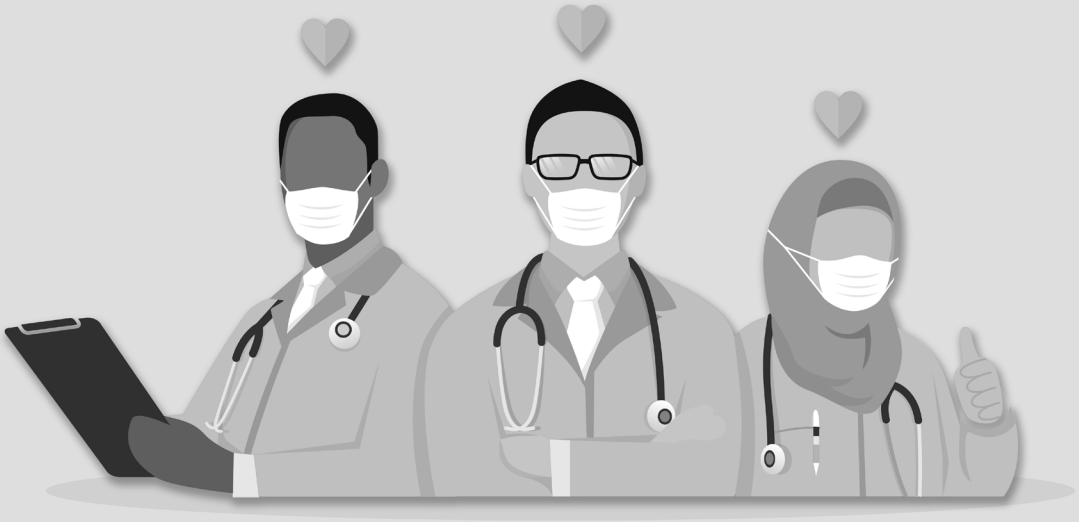

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APRESENTAÇÃO

O esforço presente na comunidade acadêmica e científica com o objetivo comum de promover saúde é uma ação que vai além da Lei orgânica da saúde, se baseando também no compromisso individual dos profissionais da área em oferecer mecanismos que proporcionem saúde à população.

Consequentemente, para se promover saúde em todos os seus aspectos, torna – se necessária cada vez mais a busca por novos métodos de diagnóstico eficaz e preciso para a mitigação das enfermidades nas comunidades. Partindo deste princípio, esta obra construída inicialmente de cinco volumes, propõe oferecer ao leitor material de qualidade fundamentado na premissa que compõe o título da obra, ou seja, promoção da saúde e consequentemente o tratamento das diversas doenças, uma vez que é cada vez mais necessária a atualização constante de seus conhecimentos.

De forma integrada e colaborativa a nossa proposta, apoiada pela Atena Editora, trás ao leitor produções acadêmicas desenvolvidas no território nacional abrangendo informações e estudos científicos no campo das ciências médicas com ênfase na promoção da saúde em nosso contexto brasileiro.

O tratamento, diagnóstico e busca por qualidade de vida da população foram as principais temáticas elencadas na seleção dos capítulos deste volume, contendo de forma específica descritores das diversas áreas da medicina, com ênfase em conceitos tais como linfonodomegalias, hipertensão arterial refratária, Doença de Alzheimer, psicoestimulante, técnicas de genotipagem, acometimento neurológico, Coronavírus, epidemiologia, oncologia, Síndrome de West; *homeostasis*, dislipidemias, SUS, fosfoetanolamina sintética, saúde do trabalhador, dentre outros diversos temas relevantes.

Finalmente destacamos que a disponibilização destes dados através de uma literatura, rigorosamente avaliada, fundamenta a importância de uma comunicação sólida e relevante na área médica, deste modo a obra “Medicina: Esforço Comum da Promoção da Saúde e Prevenção e Tratamento das Doenças – volume 3” proporcionará ao leitor dados e conceitos fundamentados e desenvolvidos em diversas partes do território nacional de maneira concisa e didática.

Desejo uma excelente leitura a todos!

Benedito Rodrigues da Silva Neto

SUMÁRIO

CAPÍTULO 18

STRESS AND DISTRESS AS BASIC PRINCIPLES OF HOMEOSTASIS AND ALLOSTASIS MODELS FOR UNDERSTANDING PHYSIOLOGICAL REGULATIONS AND RATIONAL THERAPEUTICS OF CONTEMPORARY CHRONIC DISEASES

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ABSTRACT: Man and animals are exposed to a large number of biological and environmental factors(stressors) leading to the activation of regulatory mechanisms (stress adaptation), whose variables usually return to their normal status once the stimulus(stress) has disappeared. Acute and mild stress generally induces protective mechanisms that enhance immediate survival (hormesis hypothesis) whereas, strong and sustained exposure may result in distress, a state in which an animal cannot adapt to the stressors resulting in negative effects upon its health and productivity. Homeostasis and allostasis are endogenous systems responsible for maintaining the internal stability to maintain life in an organism. In homeostasis, each stressor activates a specific regulator (homeostats) that tunes the variable to a very nearly constant. Based on homeostasis model physicians reason that when a parameter deviates from its setpoint value, some internal mechanism must be broken. Consequently they design therapies to restore the “inappropriate” value to “normal”. However, “constancy’ is not a fundamental condition for life, hence homeostasis model cannot explain the causes of most contemporary NCD. Allostasis is the process of achieving stability through physiological or behavioral change. Therefore, a mean value need not imply a setpoint but rather the most frequent demand. Allostasis considers an unusual parameter value, not as a failure to defend a setpoint, but rather as a response to some prediction. As its anticipatory action to systemic physiological regulation, allostasis reflects, at least partly, cephalic involvement in primary regulatory events. This can be carried out by means of alteration in HPA axis hormones, the autonomic nervous system, cytokines, or a number of other systems, and is generally adaptive in the short term. The allostasis model of physiological regulation, attributes diseases such as obesity, essential hypertension, type 2 diabetes and metabolic syndrome to sustained neural signals that arise from prolonged adaptation to hypervigilance and hyposatisfaction consequent to unsatisfactory social interactions. Consequently, the allostasis model would redirect therapy, away from manipulating low-level mechanisms, toward improving higher levels in order to restore predictive fluctuation. Under this model the hallmark of health is the therapeutics of contemporary chronic diseases through changing lifestyle which seems more clinically effective than drugs. Based on this, the primary and secondary care of NCD through costless and feasable lifestyle modification programs, have accomplished good results as not seen with regular medications.

KEYWORDS: Non-communicable chronic diseases, principles of treatment, homeostasis, allostasis.

1 | PHYSIOLOGICAL REGULATION OF BIOLOGICAL SYSTEMS

Man and animals are exposed to a large number of biological and environmental factors like alterations in feed and husbandry practices, climatic variables, transportation, regrouping, the therapeutic and prophylactic activities, various stressors, and so forth. Hence, the ability of the man and animal to fight against these factors is important for maintenance of their health and productivity (Rahal et al., 2014).

Any stimulus, no matter whether social, physiological, or physical, that is perceived by the body as challenging, threatening, or demanding can be labeled as a stressor. The presence of a stressor leads to the activation of neural-hormonal regulatory mechanisms of the body (Dimitrios et al., 2003).

These alterations can be viewed as a consequence of general adaptation syndrome and usually return to their normal status once the stimulus has disappeared from the scene (Akhalaya et al., 2006).

1.1 Stress and Distress

The term "stress" has been used in physics since unknown time as it appears in the definition of Hooke's law of 1658, but its first use in the biological science dates back to Sir Hans Selye's letter to the Editor of Nature in 1936 (Rahal et al., 2014). Stress is a physiological reaction that can lead to an adaptive response (Pekow, 2005).

On the basis of duration and onset, stress might be acute and chronic. The stress due to exposure of cold or heat is generally of acute type and is released with the removal of cause. Similarly, stress due to physical exercises or complete immobilization is also acute in nature. The nutritional and environmental stresses, where the causes persist for a longer period of time, are chronic stress (Rahal et al., 2014). Stress has a significant ecological and evolutionary role and may help in understanding the functional interactions among life history traits. Stress leads to a number of physiological changes in the body including altered locomotor activity and general exploratory behavior (von Schantz *et al.*, 1999; Monaghan *et al.*, 2009).

In the hormesis theory, chemicals and toxic substances that are deleterious at high doses can have a low-dose beneficial effect (Ji *et al.,* 2006; Radak *et al.,* 2008). Hence, from the hormesis hypothesis mild stresses induce protective mechanisms that enhance immediate survival (Gems & Partridge, 2008). The hormesis hypothesis is related to the effects of stress realized through the hypothalamic– pituitary–adrenal (HPA) axis, mediated by glucocorticoid secretions (Boonstra 2005; Wingfield *et al.,* 1998).

Distress differs from stress. Stress is a physiological reaction that can lead to an adaptive response (Pekow, 2005) but distress does not (Rahal *et al.*, 2014). Distress is comparatively difficult to define and generally refers to a state in which an animal cannot escape from or adapt to the external or internal stressors or conditions it experiences resulting in negative effects upon its well-being (Pekow, 2005). Strong and sustained

exposure to stress (chronic severe stress) may result in the opposite effect, possibly through continuously elevated metabolism and mobilization of energy reserves leading to higher energy negative balance (Monaghan *et al.*, 2008). Chronic severe stress may ultimately result in reduction in adaptation mechanisms, increase in the susceptibility to infection by pathogens, decline in productivity, and finally a huge economical loss (Rahal *et al.*, 2014).

1.2 Homeostasis and Allostasis

Homeostasis is the property of a system within the body of an organism in which a variable, such as the concentration of a substance in solution, is actively regulated to remain very nearly constant. The homeostatic regulation occurs despite changes in the animal's environment, or what it has eaten, or what it is doing (for example, resting or exercising). Hence, homeostasis is the regulation of the body to a balance, by single point tuning such as blood oxygen level, blood glucose or blood pH. Each of these variables is controlled by a separate "homeostat" (or regulator), which, together, maintain life. The best known homeostats in human and other mammalian bodies are regulators that keep the composition of the extracellular fluids (or the "internal environment") constant, especially with regard to the temperature, pH, osmolality, and the concentrations of Na^+, K^+, Ca^{2+}, glucose and CO_2 and O_2. Homeostats are energy-consuming physiological mechanisms. The word *homeostasis* uses combining forms of *homeo- ("*similar") and *–stasis* ("standing still"), yielding the idea of "staying the same". The concept was described by French physiologist Claude Bernard in 1865 and the word was coined by Walter Bradford Cannon in 1926.

Allostasis is the process of achieving stability, or homeostasis, through physiological or behavioral change. The concept of allostasis was proposed by Sterling and Eyer in 1988 to describe an additional process of reestablishing homeostasis, but one that responds to a challenge instead of to subtle ebb and flow. This theory suggests that both homeostasis and allostasis are endogenous systems responsible for maintaining the internal stability of an organism.

2 I HOMEOSTASIS AS THE PRIMARY MODEL FOR REGULATION

Homeostasis, from the Greek homeo, means "similar," while stasis means "stand" thus, "standing at about the same level." (The term was not coined as "homostasis" or "standing the same" because internal states are frequently being disturbed and corrected, thus rarely perfectly constant). Homeostasis describes mechanisms that hold constant a controlled variable by sensing its deviation from a "setpoint" and feeding back to correct the error. This definition has dominated physiology and medicine since Claude Bernard declared: "All the vital mechanisms...have only one object – to preserve constant the conditions of ... the internal environment". There since, homeostasis model has contributed immeasurably to the theory and practice of scientific medicine. His dictum has been interpreted literally to mean that the purpose of physiological regulation is to clamp each internal parameter at

a “setpoint” by sensing errors and correcting them with negative feedback. Based on this model physicians reason that when a parameter deviates from its setpoint value, some internal mechanism must be broken. Consequently they design therapies to restore the “inappropriate” value to “normal” (Sterling & Peter, 2004). Yet, in physiology, scientific evidence accumulates that parameters are not constant and their variations, rather than signifying error, are apparently designed to reduce error. In medicine, major diseases now rise in prevalence, such as essential hypertension and type 2 diabetes, whose causes the homeostasis model cannot explain (Sterling & Peter, 2004).

Constancy is not a fundamental condition for life. It seems past time to acknowledge that when Bernard declared constancy to be the sole object of all vital mechanisms, he went too far. Most biologists now agree that the true object of all the vital mechanisms is not “constancy” but survival to reproduce. Therefore, a mean value need not imply a setpoint but rather the most frequent demand. Some parameters are regulated quite closely. For example, the mammalian brain tolerates only small fluctuations in oxygen, glucose, temperature, and osmotic pressure. An acute insult that drives any one of these parameters beyond its design limit can trigger cascades of positive feedback that are quickly lethal. Such catastrophic departures from stability certainly require emergency (Buchman, 2002). But the purpose of such tight regulation may not be to defend “constancy” in the abstract. Rather, it may simply reflect specific design choices that optimize overall mammalian performance for successful competition. It seems past time to reevaluate the core hypothesis of the homeostasis model, that the average level of each parameter represents a “set point” which is “defended” against deviations (errors) by local feedback. This model captured much of the experimental truth in a simple “preparation” – such as an isolated organ or an animal whose brain has been silenced by anesthesia or decerebration – which were the primary experimental models for over 100 years. But regulation under natural conditions presents a response pattern that the homeostasis model cannot easily explain (Sterling & Peter, 2004).

Consider the record of arterial blood pressure measured continuously over 24 hours in a normal adult. Far from holding steady, pressure fluctuates markedly around 110/70 mm Hg for two hours. In correlation with identified external stimuli and mental states, it varies more extremely. Pressure spends about equal time above and below the steady daytime level. This pattern suggests, not defense of a setpoint, but rather responsiveness to rising and falling demand. Once the brain predicts the most likely demand, it resets the blood pressure to match. To do so, the brain directly modulates all three primary effectors: nerves signal the heart to pump faster, blood vessels to constrict, and kidneys to retain salt and water. These direct neural messages are reinforced by additional signals acting in parallel. For example, the neural system that excites the primary effectors also releases multiple hormones that send them same message. Hormones signaling the opposite message are suppressed. This pattern: multiple, mutually reinforcing signals acting on multiple, mutually

reinforcing effectors, overrides the various feedbacks that oppose change (Sterling & Peter, 2004).

Shifting setpoints might seem to describe certain cases, e.g. sustained elevation of body temperature in fever, but even here temperature is responding to specific signals that fluctuate adaptively. Recognizing such fluctuation, some authors have proposed the idea of shifting setpoints termed, “rheostasis”. The same is true for essentially all parameters: temperature, blood distribution, hormone levels, and so on. All fluctuate with different amplitudes and time constants, and these fluctuations all share a single goal. Yet the goal is not constancy, but coordinated variation to optimize performance at the least cost. This is the core idea of allostasis (Sterling & Peter, 2004).

3 | ALLOSTASIS AND THE ADAPTIVE FLUCTUATED SET POINTS

Allostasis was coined from the Greek allo, which means “variable;” thus, “remaining stable by being variable”. Allostatic regulation reflects, at least partly, cephalic involvement in primary regulatory events, in that it is anticipatory to systemic physiological regulation. This can be carried out by means of alteration in HPA axis hormones, the autonomic nervous system, cytokines, or a number of other systems, and is generally adaptive in the short term (McEwen & Wingfield, 2003). The concept of allostasis, maintaining stability through change, is a fundamental process through which organisms actively adjust to both predictable and unpredictable events. Allostasis is adaptation but in regard to a more dynamic balance, it is essential in order to maintain internal viability amid changing conditions (McEwen & Bruce, 1998a; McEwen & Bruce, 1998b).

Allostasis is underlied by six interrelated principles: (a) organisms are designed for efficiency; (b) efficiency requires reciprocal trade-offs; (c) efficiency requires predicting what will be needed; (d) prediction requires each sensor to adapt its sensitivity to the expected range of input; (e) prediction requires each effector to adapt its output to the expected range of demand; (f) predictive regulation depends on behavior whose neural mechanisms also adapt.

3.1 Principles of Allostasis

3.1.1 Organisms are designed for efficiency

Organisms must operate efficiently. Beyond escaping predators and resisting parasites, they must compete effectively with conspecifics. Natural selection sculpts every physiological system to meet the loads. No system can be “overdesigned” because robustness to very improbable loads will slow the organism and raise fuel costs. Nor can a system be “under designed” because, if it fails catastrophically to a commonly encountered load. It follows that all internal systems should mutually match their capacities. Thus our

intestinal absorptive capacity supplies sufficient fuel for our most likely energy need – with modest excess to meet unusual demands (Hammond & Diamond, 1997). Similarly, lung and circulatory capacities supply sufficient oxygen to burn the available fuel; and our muscles contain sufficient mitochondrial capacity to provide an adequate furnace (Weibel, 2000). Clearly, it would be inefficient for an organ to provide more capacity than could be used downstream, or for an organ downstream to provide more capacity than can be supplied from upstream. This aspect of organismal design, where physiological capacities optimally match, is termed "symmorphosis" (Taylor & Weibel, 1981). It holds for digestive, respiratory, and muscular systems, and also for neural systems (Sterling &Peter, 2004).

3.1.2 Efficiency requires reciprocal trade-offs

Efficiency requires that resources be shared. Otherwise, each organ could meet an unusual demand only by maintaining its own reserve capacity. To support this extra capacity would require more fuel and more blood – and thus more digestive capacity, a larger heart, and so on, thereby creating an expensive infrastructure to be used only rarely. Consequently, organs can trade resources – that is, make short-term loans. Regulation based on reciprocal sharing between organs is efficient, but for several reasons it requires a centralized mechanism: to continuously monitor all the organs; to compute and update the list of priorities; and to enforce the priorities by overriding all the local mechanisms (Sterling & Peter, 2004). For example, skeletal muscle at rest uses about 1.2 liters of blood per minute (~ 20% of resting cardiac output), but during peak effort it uses about 22 l/min (~90% of peak cardiac output), an 18-fold increase. Much of the extra blood comes from increased cardiac output, but that is insufficient and, although tissues may store fuel, such as glycogen and fatty acids, they cannot store much oxygen. Nor would it be useful to maintain a large reservoir of de-oxygenated blood because peak demand completely occupies the pulmonary system's capacity to re-oxygenate. So a reservoir of de-oxygenated blood would require a reservoir of lung, heart, etc. In turn, these would require increased capacities for digestion, absorption, excretion, and cooling. Consequently for an unstorable resource, subject to variable demand, it is most efficient to share. So, at peak demand about 10 % of the total flow to muscle is borrowed. The loan cannot come from the brain, which requires a constant supply, that if interrupted for mere seconds causes loss of consciousness. So muscle borrows from the renal and splanchnic circulations, whose individual shares of cardiac output both drop from about 20% to 1%, and whose absolute supplies fall by 4- to 5-fold. The skin circulation also contributes. Kidney, gut, liver, and skin can generally afford to lend for the short-term – depending on circumstances. For example, skin can postpone re-oxygenation – but exercise in a warm environment may require flow to skin for cooling. Gut can also postpone re-oxygenation, but following a meal it requires blood to transport digests into the portal circulation and thus needs to reclaim a higher share (Sterling & Peter, 2004).

3.1.3 Reciprocity requires central control

The brain, though it represents 2% by weight in a 70 kg man, requires 20% of the resting blood flow. This proportion is so great that when a given brain region increases activity, the extra blood is requisitioned, not from somatic tissues, but from other brain regions (Lennie, 2003). Thus within the brain itself, resources are reciprocally shared. Because the needs of muscle, gut, and skin can be irreconcilable, appropriate trade-offs between them (and all the organs) must be calculated. This requires a central mechanism, the brain, which must also enforce a specific hierarchy of priorities and shift them as needs change. When muscular effort is urgent, but you have just eaten and the environment is warm, the brain triggers a vomiting reflex; when cooling is more urgent than effort, the brain may reduce the priority for erect body and trigger the vaso-vagal reflex ("fainting"): the heart slows, vessels dilate, blood pressure falls, and muscle tone collapses. In short, the brain must decide the conditions for each loan and set the schedule for repayment. Furthermore, because such conflicts potentially threaten overall stability (survival), these solutions are accompanied by unpleasant sensations, such as nausea and dizziness, which the brain also provides. These sensations are vividly remembered in order to reduce the likelihood of repetition (Sterling & Peter, 2004).

3.1.4 Efficiency requires predicting what will be needed

Blood pressure fluctuates according to match the ever-shifting prediction of what might be needed. This is true for essentially all physiological mechanisms. Consider an additional example, control of blood glucose by insulin. This is usually presented as a core example of homeostasis: ingested glucose raises the blood level, stimulating pancreatic beta cells to release insulin, which stimulates muscle and fat cells to take up the glucose and restore blood levels to the standard ~ 90 mg/dl and, indeed a pancreas placed in vitro and exposed to glucose will release insulin. But when an intact person sits down to a meal, the sight, smell, and taste of food predict that blood glucose will soon rise, and this triggers insulin release via neural mechanisms well before freshly ingested glucose reaches the blood (Schwartz *et al.*, 2000). This anticipatory pulse of insulin signals muscle and fat cells to take up glucose, and signals the liver to cease releasing it. Thus this prediction can prevent a large rise in blood glucose. A different prediction can do the opposite, that is, can elevate blood glucose above the most frequent level. Predicting an intense need for metabolic energy can raise blood glucose to diabetic levels (Sterling & Peter, 2004).

Insulin and the myriad other hormones that regulate the fuel supply are modulated rigorously from the brain which bases its predictions on a continuous data stream regarding metabolic state that arrives via nerves from the liver and sensors in the cerebrovascular organs, such as the area postrema, and the hypothalamus (Friedman *et al.*, 1998; Saper *et al.*, 2002).

The importance and challenge of predictive regulation is best appreciated by the type 1 diabetic who tries to prevent surges of blood glucose by injecting insulin before a meal, and who must inject insulin before exercise to allow glucose to enter his muscles(Sterling & Peter, 2004).

3.1.5 Sensors must match the expected range of input

Sensors are designed to transduce a range of inputs into a range of outputs. Typically the input/output curve is sigmoid and set so that its midpoint corresponds to the statistically most probable input. The curve's steep, linear region brackets a range of inputs that are somewhat likely, and its flatter regions correspond to inputs (very weak or very strong) that are relatively unlikely. This design has a clear advantage: the most likely events are treated with greatest sensitivity and precision (Koshland *et al.*, 1982).

When input events are small, they may be amplified nonlinearly by thresholding (Field & Rieke, 2002), but most sensors amplify linearly. Overall, the design of each sensor embodies "prior knowledge", derived via natural selection, regarding the range of most likely inputs. This simple design is effective when the statistical distribution of inputs is steady. But environmental signals fluctuate enormously, for example, light intensity changes between day and night by ten billion-fold. The linear range of a visual sensor spans only ten-fold. So over the course of a day it would frequently confront a range of inputs far too large or too small for its response curve. For much stronger inputs the detector would be too sensitive, and its output would saturate; for much weaker inputs, it would be too insensitive and would miss them (Sterling & Peter, 2004).

3.1.6 Predictive regulation depends on behavior whose neural mechanisms also adapt

Prediction requires each sensor to adapt its sensitivity to the expected range of inputs. Hence, prediction must be based on sensors that are both accurate and fast with respect to the processes that they help to regulate. How sensors maintain their accuracy and speed over a large dynamic range is well understood for various neural systems, especially for vision. The basic principles seem likely to be generalizable to all sensors. However, the rate of adaptation matches the rate of changing input. Generally, the time course of predictive adaptation differs for every system and depends partly on the length of time spent under a particular load. Over hours mechanoreceptors in muscle, tendon, and ligament have reduced their sensitivities to match the persistently increased load. But then over tens of minutes, sadly perhaps, we regain our usual sense of effort as these mechanisms re-adapt to predict the next round of most likely loads (Sterling & Peter, 2004).

There are two levels of prediction: (1) most likely state in the next moment – generally best captured by the current state and its rate of change; (2) most likely time course of the

new state – generally best captured by length of time in the current state. This second factor, persistence, improves efficiency because each change requires a response, and each response has a cost. Many predictors reduce costs by anticipating regular shifts in demand. For example, circadian prediction proves so advantageous that every cell in the body uses it to regulate the expression of vast numbers of different genes according to predicted demand (Roenneberg & Merrow, 2003). On a longer time scale, seasonal variation in day length predicts average environmental temperature and food availability, performing much more reliably than local temperature. Furthermore, for migratory species day length predicts the most likely temperature thousands of miles away. Consequently, predictions based on day length have been built into the brains of many species as “prior knowledge” that profoundly regulates their physiology (Mrosovsky, 1990).

Prediction requires each effector to adapt its output to the expected range of reward. Effectors also shift their output curves to match a change in the expected range of demand. Of course, effectors change more slowly than sensors because their adaptations are more expensive. The example most familiar, because we observe it directly, is skeletal muscle. One bout of intense effort, though fatiguing, little affects the response curve. But prolonged effort over days, weeks, months gradually evokes a panoply of gene modulations: increased synthesis of proteins for muscle, bone, and connective tissue, plus corresponding shifts of metabolic and respiratory enzymes. Even so, world-class athletes known for their superior fitness, never reduce their physical demands more than momentarily, lest their effectors readapt even slightly to lower demand (Sterling & Peter, 2004).

Internal effectors also adapt gradually. For example, although the brain’s sensor of circadian time (suprachiasmatic nucleus) resets to a shift in day-length within one cycle, the liver, which synthesizes many gene products under circadian control, resets over six days (Roenneberg & Merrow, 2003). In fact all cells, via diverse molecular sensors on their surfaces (receptor proteins), regulate to meet predicted demand. Furthermore, these receptors themselves regulate in number and sensitivity to match predicted demand over a range of time scales. Typically, prolonged exposure to high levels of its natural ligand (signaling molecule) reduces receptor number and sensitivity. Note that downregulation of a receptor triggered by prolonged exposure to its ligand occurs by negative feedback. But this need not be caused by an “error”; rather the downregulation is simply a response to the anticipation of a higher level of the ligand. Thus, when blood glucose is persistently elevated and triggers persistent secretion of insulin, insulin receptors eventually anticipate high insulin and downregulate. The system learns that blood glucose is supposed to be high (Sterling & Peter, 2004). Similarly, sustained demand for elevated blood pressure teaches all effectors to expect it, and gradually adapt: arterial smooth muscle cells hypertrophy; the carotid sinus wall thickens to reduce baroreceptor sensitivity; secretory cells whose products support the pressure rise hypertrophy (renin, norepinephrine, cortisol, etc.). In short, it seems inevitable that the sustained presence of high blood glucose would gradually

reduce insulin sensitivity; i.e. cause “insulin resistance”, and thus type 2 diabetes, and that sustained elevations of blood pressure would gradually cause essential hypertension. Such changes are the appropriate adaptations to predicted demand. Predictive regulation relies on complex behavior whose neural mechanisms also adapt (Sterling & Peter, 2004).

Few of the raw materials needed for regulation are stored in any quantity. Most of the body’s sodium is in the blood and extracellular space, and sodium is lost daily, along with water, to tears, sweat, and urine. Calcium is stored within various intracellular compartments, but there it is needed for signaling and must not be depleted. Only bone can loan calcium for the short term, but for obvious reasons, the loan must be repaid. Fuel is generally stored in modest quantity as glycogen and fat, whose rapidly mobilizable components within muscle cells are just sufficient to carry a trained runner to the end of a marathon. Prolonged exertion, soon depletes stored fat and is ultimately limited by the gut’s maximum absorptive capacity – which can sustain energy consumption over basal levels by only about four-fold (Hammond & Diamond, 1997).

In short, physiological regulation is inexorably tied to replenishing. The most efficient way to update the existing stores is immediately – as an item is used. There are two reasons. First, to be depleted is unpleasant – and can be quickly lethal. Second, supplies, such as salt, water, and fuel, are not always available. The brain’s every command to consume a particular substance always accompanied by parallel commands to reduce its loss and to seek opportunities to replenish. This need to replenish generally involves a rich set of cognitive and emotional experiences. Human physiological regulation depends powerfully on a host of high-level neural mechanisms: retrieval of prior knowledge, multiple emotions, perception, planning, cooperation, and altruism. Such can thrust us back, to the root of human evolutionary success and cause us reflect on neural basis. Somewhere in the brain all the critical factors must weighed, and a plan forcefully executed. The critical site turns out to be the prefrontal cortex (Sterling & Peter, 2004).

4 I SUMMARY OF ALLOSTASIS PRINCIPLES

Allostasis describes mechanisms that change the controlled variable by predicting what level will be needed and overriding local feedback to meet anticipated demand. Allostasis takes virtually the opposite view of homeostasis. It suggests that the goal of regulation is not constancy, but rather, fitness under natural selection. Fitness constrains regulation to be efficient, which implies preventing errors and minimizing costs. Both needs are best accomplished by using prior information to predict demand and then adjusting all parameters to meet it. Thus allostasis considers an unusual parameter value, not as a failure to defend a setpoint, but rather as a response to some prediction. The allostasis model of physiological regulation, attributes diseases such as essential hypertension and type 2 diabetes to sustained neural signals that arise from unsatisfactory social interactions.

Consequently the allostasis model would redirect therapy, away from manipulating low-level mechanisms, toward improving higher levels in order to restore predictive fluctuation – which under this model is the hallmark of health (Sterling & Peter, 2004).

5 I PATHOPHYSIOLOGY FROM ALLOSTASIS APPROACH

5.1 Blood Hypertension: Adaptation To Sustained Vigilance

The homeostasis model cannot explain essential hypertension because it attributes all pathology to a "defect" – to something "broken". But the allostasis model suggests that there is no defect. More parsimoniously, it proposes that hypertension emerges as the concerted response of multiple neural effectors to prediction of a need for vigilance. When this prediction is sustained, all the effectors, both somatic and neural, adapt progressively to life at high pressure. The adaptations all seem entirely explicable from our general knowledge of signaling and regulation. Although the endpoint may be tragic, every step along the path seems perfectly "appropriate". Vigilance starts when a child is delivered from its mother's protection to the care of strangers (Sterling & Peter, 2004).

The neural signals that call for increased blood pressure also call for salty foods – which the fast-food industry ("industrial agriculture") provides in prodigious quantity. Industrial agriculture does not cause hypertension by excessively salting prepared foods; it merely obliges the public's appetite for sodium, which is driven quite appropriately by intact regulatory systems. Indeed, if under present conditions of life, the food industry were to restrict sodium, we might see the development of public "salt licks" (Sterling & Peter, 2004).

In a younger person if the predicted need for vigilance declines, effector adaptations can reverse promptly. But persistent demand leads to more profound and persistent effector adaptations. Over decades the constant call for vigilance adapts arterial muscle and carotid sinus to thicken and stiffen so that pressure rarely returns to normal levels. Probably there are also corresponding adaptations in the brain. We know now that adult synapses continuously adjust their molecular components and that "memories" are stored at all levels, even in the spinal cord (Lücher & Frerking, 2003; Ikeda *et al.*, 2003). So the many hormones that feed back to the brain to sustain high pressure probably entrain many levels to expect and support high pressure. Thus, coordinated somatic and brain adaptations generate response patterns of "established" hypertension. The hypertensive pattern, like the normal pattern, does not seem to be "defended" at a particular level. Rather it is modulated up and down, apparently according to demand, with an overall range of 140 points. This pattern suggests adaptation to chronic vigilance, and consistent with this the hypertensive pattern is absent in undisrupted preindustrial societies where children remain in contact with their parents and strangers are rare (Eyer & Sterling, 1977). Established hypertension is most common in segments of modern society where family structure is most disrupted, where children are least protected, and where they are marked from birth for suspicion and various

forms of ill-treatment. So to explain essential hypertension there is no need to postulate a "defect" in any particular regulatory pathway. Certainly we can create a hypertensive mouse by knocking out one gene or another (Wilson *et al.*, 2001; Zhu *et al.*, 2002). But we can also create hypertension and atherosclerosis in a whole colony of mice simply by introducing a stranger (Henry *et al.*, 1967).

Certainly we recognize that the variance of blood pressure within a community must be partially caused by genetic differences. But this cannot explain why blood pressures of essentially all our children rise with age. Nor why the rise is largest and most persistent in the poorest and most socially disrupted communities. Nor why African-Americans are more hypertensive than genetically similar populations in West Africa. These observations certainly point to an environmental cause (Sterling & Peter, 2004).

5.2 Obesity And Metabolic Syndrome: Adaptation To Hypo-Satisfaction

Roughly half of US adults are obese, a condition that contributes to type 2 diabetes. Obesity and type 2 diabetes jointly contribute to a constellation of pathologies termed "metabolic syndrome", which includes hypertension, glucose intolerance (diabetes), hyperinsulinemia, dyslipidemia, visceral obesity, atherosclerosis, and hypercoagulability (Zimmet *et al.*, 2001). Together these factors create a profoundly lethal cascade, and all follow the familiar epidemiological pattern: elevated with divorce, low socio-economic status, and disrupted preindustrial communities (Zimmet *et al.*, 2001; Diamond, 2003). Like blood pressure, these conditions are rising in children, where the rate of obesity has reached 15% (Hill *et al.*, 2003).

The homeostasis model cannot explain the prevalence of obesity. If metabolism were primarily controlled by negative feedback, then decreased energy expenditure would lead to decreased food intake. Yet presently in the US the opposite is so: the less we exercise, the more we eat. This conundrum could be caused by defects in the regulatory chain. For example, certain obese individuals are deficient in leptin, an important negative regulator of feeding, and when administered leptin their weight returns toward normal (Farooqi *et al.*, 2002). But, just like hypertension, specific defects in energy regulation are rare. They account for only a minor fraction of obesity and for none of its striking increase (Hill *et al.*, 2003).

5.3 Type 2 Diabetes

Homeostasis cannot explain the growing prevalence of type 2 diabetes. Its core feature, insulin "resistance", involves changes at many levels, including decreased concentrations of insulin receptors, kinase activities, concentration and phosphorylation of IRS-1 and –2, PI(3)K activity, glucose transporter translocation, and the activities of intracellular enzymes. Although these changes are loosely termed "defects" (Saltiel & Kahn, 2001), they do not arise from mutant alleles, so "defect" denotes, not their origins, but rather their unwanted effects.

5.4 Obesity and Insulin Resistance : Vigilance that makes adaptive senses

The allostasis model can explain both obesity and insulin resistance without postulating any true defect. The rise in obesity and type 2 diabetes has been attributed to "thrifty genes". From this theory some population were selected to "eat up" in times of plenty to protect against times of famine (Diamond, 2003) as happened with certain human groups among Pacific Islanders that have suddenly changed from food scarcity to plenty. This implies that body fat is not regulated to a setpoint, but varies according to some prediction – in this case, future hunger. This theory would be entirely consistent with the allostasis model, but there may be an additional explanation. Consider that for these groups the sudden appearance of plentiful food is accompanied by the equally abrupt dissolution of the entire culture. Consequently, obesity is only one disorder of many that accompany disruption of a preindustrial society. The standard signals for vigilance (such as cortisol), which raise the appetite for sodium, also raise the appetite for carbohydrate and fat (Schulkin *et al.*, 1994). This makes adaptive sense – if we will soon need more salt, we will also soon need more fuel. Elevated cortisol also shifts the distribution of fat deposits toward the viscera – one feature of metabolic syndrome. And when chronically high levels of carbohydrate evoke chronically high levels of insulin, its receptors and their downstream mechanisms naturally reduce their sensitivities, just as every signaling system responds to prolonged, intense stimulation – the input/output curve inexorably shifts to the right (Sterling & Peter, 2004).

Cortisol and related signals are elevated, not only during hypervigilance, but also during states of hyposatisfaction – when outcomes prove less than expectations. Because satisfaction cannot be stored, it must be continuously renewed. So if its potential sources become constricted, the brain must inevitably rely on those that remain: people needing a pulse of satisfaction will try to find it somehow (Sterling & Peter, 2004). For those of higher socioeconomic status there are opportunities for satisfaction in work, achievement, and money. Mono-pursuit of such opportunities tends to spiral out of control ("workaholism", "type A" behavior, etc). This may occur especially when expectations inculcated by the family as "prior knowledge" are so high as to be intrinsically unsatisfiable. Another likely factor is that a stimulus which initially releases dopamine adapts, limiting the satisfaction obtainable from its repetition. For people of lower socioeconomic status potential sources of satisfaction are less available, but food is abundant and cheap. So the allostasis model suggests that the brain overrides local negative feedback (metabolic satiety signals) – just as it overrides the negative feedback that would counter commands to raise blood pressure – and people eat. For the reasons just cited, satisfaction is fleeting – so people eat even more (Saper *et al.*, 2002; Schultz, 2002).

Alcohol and drug addictions follow a similar pattern and apparently share many of the same mechanisms (Wise, 2003). For example, the neuropeptide NPY enhances feeding, and is also abundant in brain areas mediating these drug addictions. The acute

effect of NPY resembles alcohol in reducing anxious behavior, and it is also associated with developing alcohol and cocaine dependence. Similarly leptin, identified primarily with feeding and energy balance, contributes to hypertension. Thus, there is considerable cross-talk between these systems along brain pathways that serve satisfaction (VTA- amygdala-accumbens-prefrontal cortex) (Sterling & Peter, 2004).

Among Native Americans, Australian Aborigines, Inuit, and so on, the rise in obesity and type 2 diabetes invariably accompanies rises in essential hypertension, alcoholism, drug addiction, suicide, and murder (Eyer & Sterling, 1977). Furthermore, the same correlations are found in modern societies: the highest rates of all these afflictions appear in the most disrupted populations, those with the worst life experience, the lowest expectations, and the least hope. Thus over the period of rising racial segregation in urban neighborhoods and schools, the prevalence of obesity in predominantly black elementary and middle schools has tripled (Gordon-Larsen *et al.*, 1997).

In summary, the allostasis model attributes the pathogenesis of hypertension and metabolic syndrome to prolonged adaptation to hypervigilance and hyposatisfaction. The impact is strongest among populations with the best reasons for vigilance, the narrowest range of satisfactions, and expectations that are least often met (Sterling & Peter, 2004).

6 I TREATING HOMEOSTASIS AND ALLOSTASIS MODELS

6.1 Treating "Low-Level" Targets: Poly-drugs, Iatrogenesis and Drug-addiction

Homeostasis treats low level targets. Following the homeostasis model, physicians try to restore each parameter to what they consider an "appropriate" level. Therefore, hypertension is treated with drugs that target the three primary effectors of elevated pressure: (i) diuretics to reduce blood volume; (ii) vasoconstrictor antagonists to dilate the vascular tree; (iii) heart rate antagonists to reduce cardiac output. The pharmaceutical industry continues to target myriad molecules that regulate these three mechanisms, and fundamental research widely promises to identify new targets (Sterling & Peter, 2004). The same is true for obesity. A review lists six neuromodulators that increase feeding and ten that decrease feeding, and then concludes, "a multi-drug regimen that targets multiple sites within the weight-regulatory system may be necessary to achieve and sustain weight loss in many individuals" (Schwartz *et al.*, 2000). The same strategy is proposed for type 2 diabetes and metabolic syndrome (Moller, 2001) and for drug addictions (Laakso *et al.*, 2002).There are three problems with targeting low-level mechanisms.

First, each signal evokes multiply cascaded effects, so even the most specific molecular antagonist will cause a cascade of effects. For example, in hypertension the angiotensin converting enzyme affects all of angiotensin's myriad downstream targets (arteriolar muscle, kidney, and multiple brain sites), and so also does its widely prescribed

inhibitor (Sterling & Peter, 2004). Similarly, in type 2 diabetes one effect of hyperglycemia is to elevate the signaling molecule, diacylglycerol. This triggers protein kinase C, and thereby a host of signals, all of which contribute to vascular pathology. Although it might seem advantageous to antagonize an early step, such as the activation of protein kinase C, myriad other cascades with beneficial effects would also be affected and, it turns out that because of such cascading effects, low level inhibitors and antagonists tend to be strongly iatrogenic (Buchman, 2002; Sterling & Eyer, 1981).

Second, the variables targeted for treatment are being driven to their particular levels by concerted signals from the brain in response to predicted needs. Consequently, if one signal is suppressed by a drug, the brain compensates by driving all the others harder. Thus, when blood pressure is treated by a diuretic to reduce volume, there are compensatory increases in heart rate and vasoconstriction. These can be treated in turn by beta- adrenergic antagonists, calcium channel antagonists, etc. (Carretero & Oparil, 2000; Sterling & Eyer, 1981). But adding more drugs to a complex system increases the frequency of iatrogenesis. This is why proposals to treat obesity by a multi-drug regimen at multiple brain sites or to screen 417 genes as drug targets for obesity seem implausible.

Third, there is a cost to performance in clamping a variable to some target level by blocking the effectors designed to modulate it. Clamping renders that variable insensitive to predicted need, which oposes the whole point of physiological regulation. Thus clamping blood pressure low with a beta-blocker commonly causes “exercise intolerance” – inability to increase cardiac output when it is needed (Sterling & Peter, 2004).

For all of these reasons, less than 25% of hypertensive patients in the US are controlled. The major problem is considered to be “the very high rate of discontinuance or change in medications: 50-70% ... within the first six months... “ (Carretero & Oparil, 2000). These high discontinuance rates are considered to reflect, among other factors, “a combination of adverse drug effects, cost of drugs, and poor efficacy” (Carretero & Oparil, 2000).

These problems also apply to pharmacotherapy for mental disorder. Certainly drugs are better than lobotomy: they can be titrated and are reversible over the short run. But when applied for long periods, the “antipsychotic” drugs, which primarily antagonize various dopamine receptors, cause motor disorders. These “tardive” (late appearing) dyskinesias eventually occur in most patients and persist after the drugs are withdrawn. Beyond this devastating iatrogenic effect, drugs that work by antagonizing the major modulators of the nucleus accumbens, amygdala, and prefrontal cortex will, like beta-blockers for blood pressure, reduce responsiveness. Such drugs would be predicted to cause in stability of intent and to flatten affect. In fact they do, and this is a major reason why patients often refuse to take them (Sterling & Peter, 2004).

6.2 The "Higher-Level" Interventions

The allostasis model defines health as optimal predictive fluctuation. 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. A shift in the probability of demand should shift the response, and when the prediction reverses, so should the response. A system becomes unhealthy when, high demand predominates for long times, effectors adapt so strongly that they cease to follow promptly when the prediction reverses and, system does not return to the initial state (Sterling & Peter, 2004).

By standard pharmacotherapy, drugs can force the response back to the original level, despite continued prediction of high demand, but this compresses responsiveness. While demand stays high, drugs that antagonize key effector mechanisms force the response distribution back toward its initial mean. But 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. This is a common complaint of patients on anti-hypertensive and psychotropic medications (Sterling & Peter, 2004).

A more rational goal of intervention would be to shift the predicted distribution of demand back toward its original level. This would allow the effectors to naturally reestablish flexible variation around the predicted lower demand, thus preserving the range of responsiveness. In other words, by 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 (Sterling & Peter, 2004. This seems to work very much for hypertension while considering that the current authoritative recommendations for treatment are no longer drugs but: (i) weight loss; (ii) exercise; (iii) moderate alcohol consumption; (iv) diet reduced in sodium and fat and increased in calcium, potassium, and fiber; (v) cease smoking (Carretero & Oparil, 2000; Burini et al. 2018; Polo et al. 2019).

Weight loss is strongly correlated with reduced blood pressure and is considered to be the most effective of all nonpharmacological treatments. Moderate exercise, such as brisk walking or bicycling thee times per week, may lower systolic pressure by 4-8 mm Hg. The dietary recommendation is based on the "DASH" study, which found overall reductions in blood pressure of 11.4/5.5 mm Hg to a diet rich in fruits, vegetables, and low-fat dairy products, with further reductions of pressure to reduced sodium intake. These reductions are said to be "comparable to or greater than those usually seen with monotherapy (i.e., 1 drug) for stage 1 hypertension". But as the DASH study notes, long-term health benefits "will depend on the ability of people to make long-lasting dietary changes, including the consistent choice of lower- sodium foods" and "upon (their) increased availability" (Sacks *et al.*, 2001). This requires, in effect, a sustained victory in the prefrontal cortex of abstract

knowledge about what is “good for you” over all the unsatisfied appetites that cause the problem in the first place. Hold onto your McDonald’s stock (Sterling & Peter, 2004).

The most successful interventions do not deny the sense of need. Rather, they find ways to satisfy it by enlarging positive social interactions and revivifying the sense of connectedness. In the case of coronary heart disease, when patients combined diet and exercise in a group context with a charismatic leader, atherosclerotic plaques regressed over a year, as established by angiography (Ornish *et al.*, 1990). This is not to argue against treating any mental disorder with a drug. Almost certainly, some disorders will be found to arise from specific molecular defects, just as specific mutations of ion channels, gap junctions, and signaling enzymes, etc. are being identified as causing various neurological disorders. But just as those defects are fairly rare, and just as molecular defects account for a minor proportion of hypertension, there is likely to be a rather large residual group that will be considered “essential mental illness” – arising from the same core problems of social disruption/disconnection(Sterling & Peter 2004).

This seems particularly applicable to the large group of boys now diagnosed with “attention-deficit, hyperactivity disorder” (ADHD). The prevalence of this diagnosis among boys in the U.S. has reached ~10-30% and it varies inversely with socioeconomic status. The standard drug treatment is methylphenidate – “Ritalin” – an amphetamine analog, or dextroamphetamine. These drugs do help a rambunctious youngster to settle down in the classroom and concentrate for longer periods than he could normally manage. This should not be a surprise because these are the drugs that a street addict takes to obtain his small satisfactions – to quiet his restless prefrontal cortex and, these are the drugs that the long-distance trucker takes to concentrate on the road. So it seems entirely consistent that a boy dosed with amphetamine can concentrate on the assigned task. But over the long term these drugs will certainly cause brain adaptations whose specific consequences cannot be foreseen. This example seems especially poignant because it arises from disrespecting our greatest evolutionary advantage: our intrinsic diversity of talent and temperament. A proto-scholar might sit still effortlessly in a classroom, whereas a proto-navigator or proto-comedian might not. The allostasis model would not administer the very drugs upon which (outside the classroom) we have declared “war”. Rather it would investigate the possible causes of a youngster’s restlessness and would intervene by finding activities – beyond sitting still with a book – that would absorb him(Sterling & Peter 2004).

6.2.1 Physiological mechanisms of high-level intervention

The allostasis model hints that the biggest improvements in health might be achieved by enhancing public life. The guiding principle would be: do everything that promises to reduce the need for vigilance and to restore small satisfactions. Enhance contact with nature by building more parks and by providing communal opportunities to garden – i.e. not

just to look at but to grow flowers and vegetables. Enhance opportunities to walk and cycle by restricting automobile traffic. Prevent this restriction from becoming an annoyance by improving public transportation. Encourage broader participation in sports especially among youth – by constructing public facilities for gymnastics, skating, skate-boarding, climbing, and swimming (Sterling & Peter, 2004).

Improve work by acknowledging that no human can be satisfied by performing an unvarying task for eight hours a day, 40 hours per week, 50 weeks per year. Companies, and now even the National Institutes of Health, play a recording, "this phone call may be monitored for purposes of quality control". What this implies, of course, is that the task is so uninteresting that the operators need to be threatened with every call that their supervisor might be listening. For workers at the computer, every keystroke can be similarly monitored. Such humiliating and alienating procedures were introduced recently and could easily be eliminated. The astronomical disparities of income are also recent and could be narrowed while still preserving incentives for the more energetic and clever. Such proposals are well within our capacity to organize and implement – for they would benefit the rich as well as the poor by reducing everyone's need for vigilance and by expanding everyone's range of small satisfactions (Sterling & Peter, 2004).

7 | LIFESTYLE CHANGING

Therapeutic lifestyle change seems yet more clinically effective than drugs. The combination of exercise with dietary changes is more effective than each one alone. The effectiveness of the dietary changes is based on low-energy dense diets mainly providing high dietary fiber intake. The state-of-the-art nutritional science readily explains the metabolic benefits of a (modest) restriction of carbohydrates, a lack of high–glycemic index products, a low W-6 over W-3 fatty acid balance, and a reduction of salt intake in patients with the NCDs. Additionally, increased physical activity is considered the cornerstone of recommendations for treating NCDs. So far increased physical activity seems more effective with aerobic exercises (and increased cardiorespiratory fitness) than strength exercises. However, aerobic interval training, strength training, or the combination of both have beneficial effects on physiological abnormalities associated with NCDs. Costless lifestyle modification programs applied to community based adults have promoted eutrophy, blood hypertension, T2D and Metabolic Syndrome reductions not seen with regular medications (Burini et al. 2013; Burini et al. 2013b;Burini et al. 2017b;Burini et al. 2016; Burini et al. 2020).

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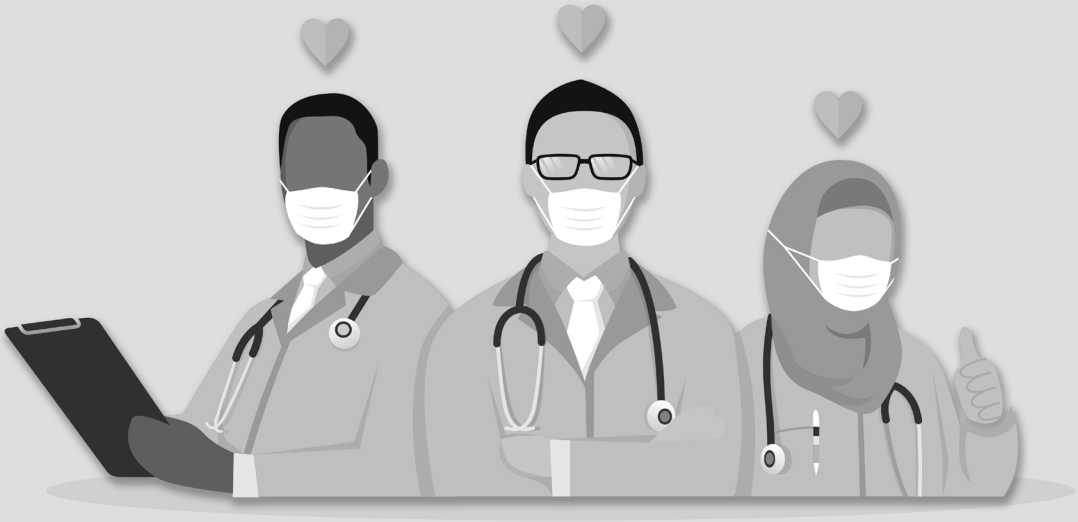

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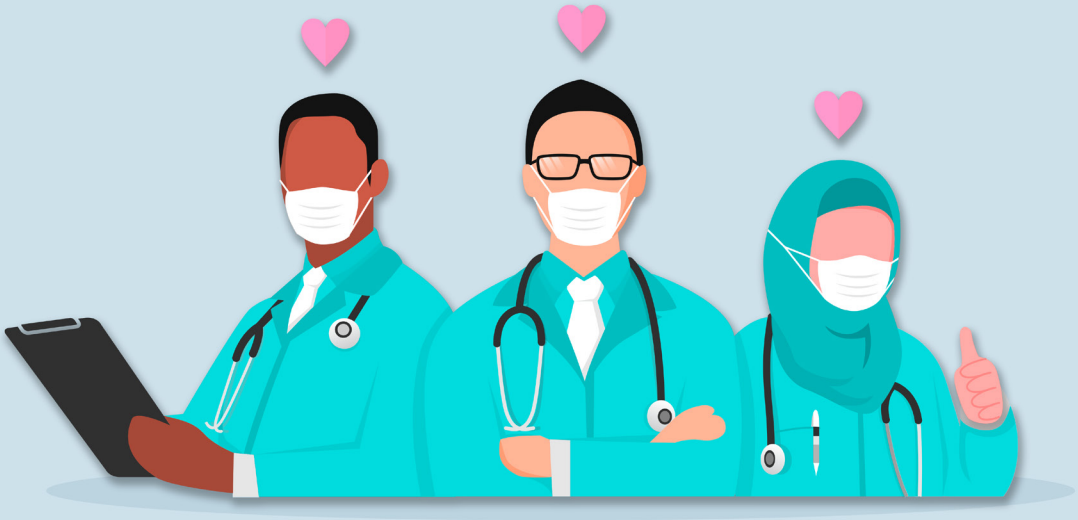

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