

# Coronary microvascular and endothelial function regulation: Crossroads of psychoneuroendocrine immunitary signals and quantum physics [Part B]

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## Abstract [Part B]

Stress is the key element that unites all the influences that have a cellular impact in the coronary microcirculation, determining serious consequences for health. In particular, mental stress does not differ from the physical stress and is always part of the biological processes that are examined in the research and daily clinical practice. Many cardiovascular diseases occur after a long process of stress, compensation and exhaustion, after accumulating some allostatic load. The stress reaction is common both at a macroscopic level both at the cellular level. We move forward considering the biological cellular balance, especially cardiovascular one, in molecular and atomic terms, with reference to the newest achievements in the field of quantum physics. The above leads inevitably to raise three important issues that must be solved in order to progress effectively in scientific research.

## The link between stress, cardiovascular disease and endothelial function

### Chronic stress is associated with the pathogenesis of CVD and increases CVD mortality

A wide variety of treatments against atherosclerosis-based CVD have been introduced by medical science during past years, with a significant reduction in mortality associated with these diseases. However, ischemic CVD remains a leading cause of death worldwide.

In addition to traditional risk factors such as dyslipidemia, hypertension, smoking, diabetes, obesity and physical inactivity, stress is thought to be a pivotal. Several types of stress are involved in the development of CVD, including oxidative stress, mental stress, hemodynamic stress and social stress.

A very interesting thing to note is that the condition of stress is the basis of each of the traditional cardiovascular risk factors [1-17].

The common effect of all these factors is to induce oxidative stress [18] in the vasculature leading to inflammation, endothelial dysfunction, atherogenesis, hypertension and remodeling of blood vessels.

Meanwhile, mental stress is a well-known major contributor to the development of cardiovascular disease [19-25]. It's the case of depression [26] which, for example, induces inflammation [27,28,29], oxidative stress, increases platelet reactivity [30,31,32], extends QTc interval [33], it is accompanied by an activation of the endocannabinoid system [34, 35-40] or induces mental stress myocardial ischemia. Even depression alone could lead to coronary artery calcification [41]. Moreover, Redmond *et al.* described that perceived stress is associated with incident coronary heart disease and all-cause mortality [42]. As shown by Lazzarino *et al.* mental stress is associated with cardiac cell damage with detectable plasma levels of troponin-T (cTnT) using

high-sensitivity assays in healthy subjects, independently of coronary atherosclerosis [43]. As we will see, the concept of "personality" is intimately linked to the concept of mental stress. Some personality patterns [44], that is, depressive or aggressive moods, are linked with higher incidence of cardiovascular diseases [45-47] through chronic stress axis activation [48,49]. On the contrary, a positive affect and good interpersonal relations [50] rebalance the neuroendocrine stress axis, reduces inflammation and improves cardiovascular balance [51-54].

Heart and vessels are constantly exposed to hemodynamic stress by the blood flow and/or pulsation, and hemodynamic stress exerts profound effects on the biology of vascular cells and cardiomyocytes [55]. And it's quite intuitive considering that in a state of mental/ social or physical stress, the hemodynamic stress increases as a simple result of the nonspecific physiological stress response (increased sympathetic tone, increased blood viscosity and thrombogenesis etc.) [56].

In addition, social stress (due to a lack of social support [57], poverty or living alone, unemployment [58]) has a negative impact on the incidence and prognosis of cardiovascular disease [59].

Furthermore, there are interactions between mental, oxidative and hemodynamic stress. The production of reactive oxygen species

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is increased under high levels of mental stress in close association with oxidative stress. These factors of the stress response and their interactions play central roles in the pathogenesis of atherosclerosis-based cardiovascular disease [60]. Their action is associated with epigenetic changes (change of some circulating miRNAs, with relative change of the expression of inflammation genes) that occur rapidly after exposure to a stress, as demonstrated in animal models by Cho *et al.* [61].

### **The mind is the area where the “danger” is perceived and triggers and modulates stress reactions. Brain and mind: new insights from modern neurobiology**

The relationship between brain and mind has philosophical, religious, scientific and practical implications. Philosophers and scientists have wrestled with the so called mind-body problem for millennia [62,63]. Nowadays, technical and cultural advances in neurosciences lead us to consider the brain and its neurons either as the basis from which thoughts and various types of consciousness arise, or as the destination of the psychological functions rising from its circuits. Neural circuitry and plasticity, molecular profiles, and neurochemistry can be changed by experiences and thoughts, which influence behavior as well as neuroendocrine and autonomic function [64].

Psychological stress influences biological systems that can damage the brain [64], the immune system [65] and dysregulate hormones and metabolism [66,67]. The activity of biological systems can modify our thoughts: for example, depression produces inflammation and inflammation itself could cause depression [28,68].

The brains of subjects who are awake but at rest show spontaneous, synchronous, low-frequency oscillations. The mental processes of attention and thinking are increasingly becoming associated with the activity in different distributed brain regions (Figure 1-A). A task-negative, or default mode network (DMN) has been associated with independent, spontaneous thought processes, also known as mind wandering [69,70]. The activity of this system increases during self-oriented thinking, e.g. during a resting state, but decreases during externally oriented attention and specific cognitive tasks [71].

Many studies illustrates the functional significance of DMN suppression deficits in severe mental illness [69]. The continuous activation of this system is therefore related to illness.

The building circuits of the DMN (which comprises the cortical midline structure, lateral parietal and temporal areas as well as the posterior cingulate cortex and the medial prefrontal cortex [69]) are linked with the limbic system and amygdala, and are the same involved in the response to stress, fear or anger and all related neuroendocrine products and effects [72] (Figure 1-B).

As we described earlier, some areas of the limbic system within the DMN, receive afferents cardiac fibers which run through the vagus nerve [73,74,75-79]. This is the anatomical basis of the so called “neuro-visceral integration model” of emotion regulation [75]. According to this model, verified by Thayer *et al.* since 2000 [80], the heart plays a central role in cognitive [81], perceptual [82,83] and emotional [74,84,85] functions, actively regulating neuronal activity and brain responses.

The default mode of humans appears to be that of mind-wandering, which correlates with unhappiness, fear and neuroendocrine production in the stress axis, with the activation of brain network areas associated with self-referential processing. The default-mode

functioning of the brain continues to compare past experiences with anxiety and fear for the future, fearing that what made us suffer and could make us suffer will not occur [86], sowing the seeds of future CVD, as depicted in Figure 2 (please see “allostatic load”, below).

Conversely, a task positive network has been associated with various attentional, present moment, and task-related processes, and is active during rest in an anticorrelated manner with the DMN [87,88,89]. This large task-positive network can be subdivided in distinct subnetworks, in particular the salience and executive networks [90].

The salience network is thought to be involved in the immediate, present moment processing or detection of relevant stimuli, and involves the dorsal anterior cingulate cortex and bilateral anterior insula [90,91]. The executive network, also referred to as the frontoparietal attention network, consists of dorsolateral prefrontal cortex and posterolateral parietal regions, and is involved in controlling attentional resources to deal with immediate or future demands [90,91].

As stated, psycho-physical stress exacerbates the pathogenesis and progression of cardiovascular diseases. Basic research indicates that the Transcendental Meditation® technique produces acute and longitudinal reductions in sympathetic tone and stress reactivity through DMN downregulation, decreasing cardiovascular risk factors and all-cause morbidity and mortality [92].

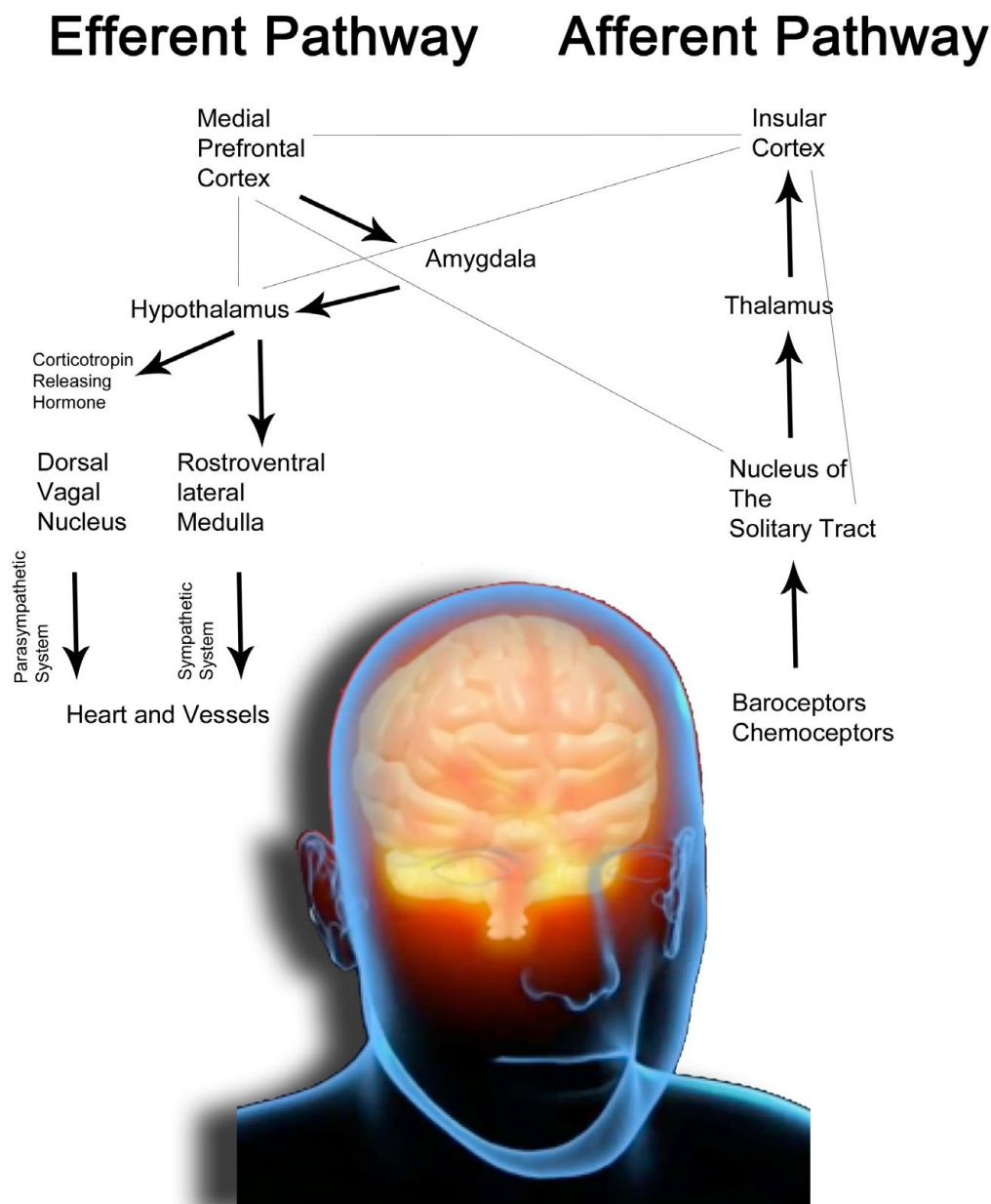
Music appreciation modulates DMN activity too [93]. As described by Kay *et al.*, patients suffering from Alzheimer’s disease or temporal lobe epilepsy exhibit changes within the DMN circuit. In this context music is able to switch off neural firing, interrupting epilepsy [94,95].

The activation of the DMN and mind-wandering, could be either a quite conscious process, as in the case of depression, which independently from other CVD factors (and even alone) could lead to coronary artery calcification [41], or unconscious, because an inflammatory state or even what we eat could cause depression or, more in general, influence our mood and relative thoughts [27,96,97]. The study and future researches on CVD have bear in mind the PNEI connections and their constant and mutual influences, as a single, integrated system of interaction with the environment [72]. Many trials of psychotherapy aimed at preventing cardiovascular risk, failed [48] probably because it was ignored the prospect of PNEI network. From this point of view, in fact, is not possible to treat depression with psychological-cognitive-behavioral therapies without trying to solve any underlying inflammatory or endocrine organic problem, which continues to fuel it.

However, it is possible to act on different fronts of the PNEI network, improving the health status of patients (with meditation, listening to particular kinds of music, with moderate physical activity, nutrition, herbal medicine and attention to social and physical environment in addition to standard therapies) [98].

### **CFR is reduced in most of CVD**

Endothelial function is the backbone of cardiac functioning, so much so that its dysfunction is described in all cardiovascular diseases. In fact, it could be detected an endothelial function dysregulation in case of arteriosclerotic/ischemic disease [99], valvular disease [100] (aortic stenosis [101-107], mitral valve disease [108-110], mitral valve prolapse [111]), atrial fibrillation (in this case atrial endothelial impairment causes thrombogenesis through TLR-4 signalling) [112], ventricular tachycardia [113], ventricular septal defect [114] and cyanotic congenital heart disease [115], left apical ballooning



**Figure 1A.** The drawing schematically represents the anatomical organization of the autonomous nervous system in humans. The Default Mode Network comprises cortical areas (the cortical midline structure, lateral, parietal and temporal areas, the posterior cingulate cortex and the medial prefrontal cortex) connected to the amygdala and limbic system. Heart and vessels function is finely adjusted through parasympathetic and sympathetic neural stimulations and hypothalamic hormones which constitute the efferent pathways of the system (for simplicity we quote only corticotropin releasing hormone, which mediates the release of cortisol, the main stress hormone).

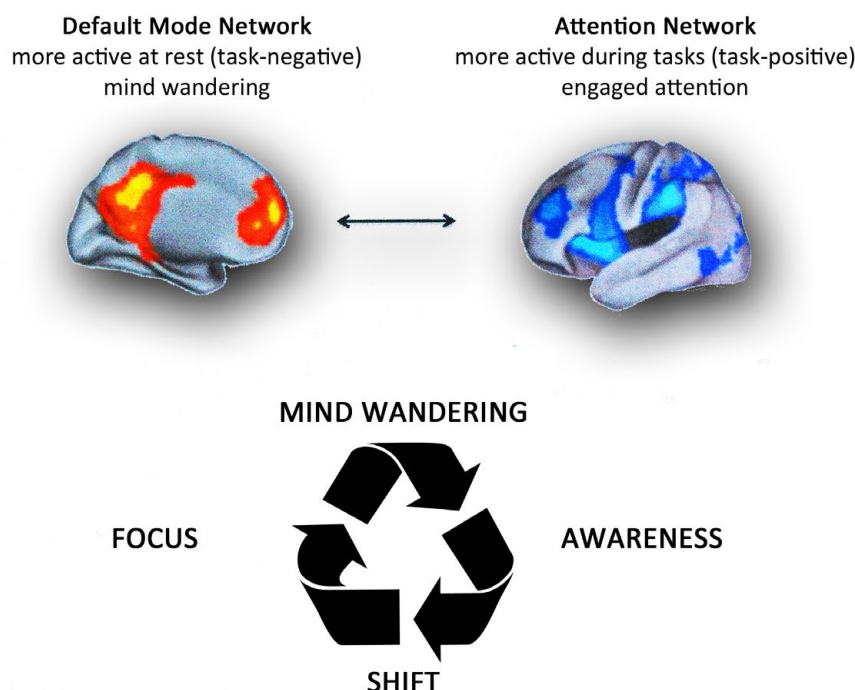
syndrome [116], dilated cardiomyopathy [117,118,119,120] and heart transplantation [121,118,122].

As previously stated, this parameter is therefore of paramount importance from a prognostic point of view as well as able to predict the onset of a cardiovascular disease [123].

### Stress leads to endothelial dysfunction

All the factors that come into play in the stress reaction determine a endothelial dysfunction [124,125,126]. From the point of view of PNEI

network it is easy to see how even the only mental stress can cause an alteration of endothelial function in the coronary district [127,128-132], and beyond [133], that is transient [134] or persistent [135] depending on the duration and severity of mental stress [136]. Furthermore, it is interesting to notice that higher levels of both cognitive and somatic depressive symptoms are associated with a higher propensity to develop myocardial ischemia with mental stress, but not with physical (exercise or pharmacological) stress [137].



**Figure 1B. Top. Brain networks associated with mind wandering and attention.** The brain can be divided into two-large scale distributed network: the default mode network, in which is associated mind-wandering activity, and the attention network that is associated with focused states demanding attentional resources. **Down. The process of attention during meditation.** A theoretical model of dynamic cognitive states experienced by a non-expert practitioner during a session of meditation. When attempting to sustain focus (FOCUS) on an object (breathing, mantra, images, etc.), an individual inevitably loses this focus and experiences wandering of attention (MIND WANDERING). At some time during mind wandering, the practitioner becomes aware that his/her mind is not on the object (AWARENESS), at which point he/she disengages from current train of thought and shifts attention back to the object (SHIFT), where it stays focused again for some period of time (FOCUS). With practice, the time spent during the focused and conscious thought increases. There are various methods of meditation with a common experiential goal. It's like climbing a mountain: there are several trails, slopes, ascent velocities and path lengths, but the summit is the same. Modified from Schmidt *et al.* [91].

## The allostatic load and the programming of CVD

After this long introduction, necessary to understand the game of influences acting in every moment of our lives on the endothelium, we can connect into a single mechanism all these details (Figure 2). This overview will allow us to clarify and suggest what can be done in terms of prevention and treatment of cardiovascular disorders, as well as what type of research is needed for this purpose.

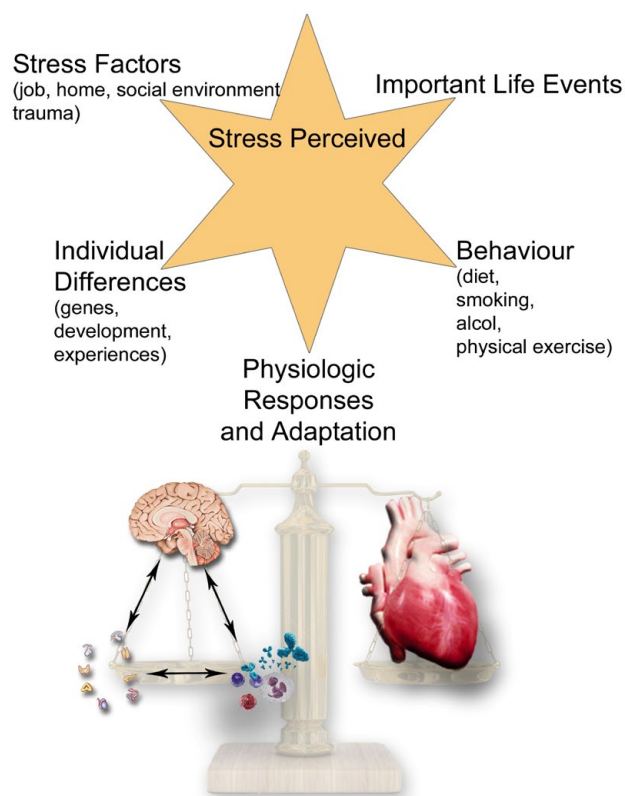
Every human being is born inheriting from their parents not only the genetic makeup, but also how to express it. In particular, we born with a precise stress-axis programming [138,139-142]. As described by Harris *et al.* “an adverse foetal environment is associated with increased risk of cardiovascular, metabolic, neuroendocrine and psychological disorders in adulthood. Exposure to stress and its neuroendocrine and immune mediators may underpin this association. In humans and in animal models, prenatal stress, excess exogenous glucocorticoids or inhibition of 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (HSD2; the placental barrier to maternal glucocorticoids) reduces birth weight and causes hyperglycemia, hypertension, increased HPA axis reactivity, and increased anxiety-related behaviour. Molecular mechanisms that underlie the “developmental programming” effects of excess glucocorticoids/prenatal stress include epigenetic changes in target gene promoters. In the case of the intracellular glucocorticoid receptor (GR), this alters tissue-specific GR expression levels, which has persistent and profound effects on glucocorticoid signalling in certain tissues (e.g. brain, liver, and adipose). Crucially, changes in gene expression persist

long after the initial challenge, predisposing the individual to disease in later life. Intriguingly, the effects of a challenged pregnancy appear to be transmitted possibly to one or two subsequent generations, suggesting that these epigenetic effects persist [141]”.

Thus, each individual is already born inheriting some resistance or vulnerability to stress: in practice, this means that some people are inclined to consider something as a danger or as a threat, and will have a greater tendency to be worried about the future, to get angry or feel guilty [143]. Then, on this ground, will act on the course of life, being able to change the situation for better or for worse. We already cited that the epigenetic signatures are stable but reversible. Despite the “stress thermostat” is already programmed in the course of intrauterine life, it can be further modified by each individual in a lifetime. Obviously they will experience acute and chronic stress of various kinds, physical or psychosocial, constantly activating DMN circuits and the stress axis.

From the point of view of the PNEI-network and of the stress system, we have to change the concept of “homeostasis” to “allostasis”. Over 60 years ago, Selye recognized the paradox that the physiologic systems activated by stress can not only protect and restore but also damage the body [144]. The long-term effect of the physiologic response to stress is called “allostatic load” [145]. “Allostasis” — the ability to achieve stability through change— is critical to survival [144]. In fact, after a solicitation of any kind, our PNEI-system adapts learning and changing its functions being more responsive in the event of recurrence of a stimulus of the same type. Is the case of the nervous





### Allostatic Load and cardiovascular health

**Figure 2. The allostatic load and the chronic building of CVD.** The picture painted shows that the body is able to respond adaptively to the adverse circumstances that threaten its integrity through activation of the sympathetic-adrenergic and the HPA systems. The stress response, which Selye called “general adaptation syndrome” or GAS, consists of a stereotyped sequence of three distinct phases: an *alarm phase* where the coordinated action of neurotransmitters and hormones promotes the rapid mobilization of energy resources available to face the stressor; a phase of *resistance*, in which the body’s response reaches a stable equilibrium and the manifestations typical of the alarm phase disappear, to reappear in the final stage of *exhaustion*, in the case the stimulus persists and physiological resources are depleted. A stressor can be anything that can evoke GAS whether physical (trauma, thermal injury, infection and poisoning) or psychological. Although essentially non-specific, the GAS can be realized in a variety of polymorphic biological responses depending on the nature, location and extent of the damage induced by various stressors and based on the individual’s genetic and epigenetic background. In fact, the activation way of the stress axis can be epigenetically inherited from parents and over the generations. The GAS may represent a pathophysiological basis common to many diseases and biological processes apparently unrelated. “Adaptation” and “damage”, in any organ, are two sides of the same coin: the stress phenomenon and its network.

In truth, since the 70s of the last century, Mason *et al.* [463] shifted the focus on the interactions between stressful stimuli and psychological homeostasis, criticizing the concept of the non-specificity of the stress response, documenting how the typical elements of GAS undergo significant changes depending on the context, history and personal characteristics of the individual. Mason notes that when removing the psychological concomitants of anxiety associated with the stressor, disappears also the GAS reaction: the psyche overlaps and is connected to the “biological machine” in the regulation of body functions. A few years later, in 1988, Sterling and Eyer [464] propose, for the first time, the concept of “allostasis”. They observe that in response to environmental stress, physiological parameters are changed in line with the behavioral states, which, in turn, correspond to specific states of brain activity. The sensory input from any form of stressors, physical or psychological, are firstly processed by the brain to influence any kind of physiological response and these inputs can be changed from the expectations and individual evaluation processes [465]. Subsequently, Chrousos, Goldstein [466,467] and Sapolski [468] described as a physiological system disrupted by a stressor responds “learning” by the event itself and readjusting its operating parameters around new reference set-points (*allostatic accommodation*). The body under stress does not bother to return to its “normal” values of balance, but sets in motion a new balance, evolutionarily advantageous, able to put him in the best possible condition to face an environmental danger, real or imagined that is.

A common example: the blood pressure rise during the day according to the activities that take place and the state of individual alert. Endocrine and cardiovascular systems anticipate future needs, to respond to a possible sudden request. Obviously, the anticipation also involves psychological states of anxiety, apprehension, concern and regulation of molecules as cortisol and adrenaline [469]. It’s the brain that evaluates and decides whether a particular situation merits a state of alert; psycho-cognitive functions, such as anticipation, risk assessment, coping strategies, memory, are integrated in the processes of physiological regulation [470]. But stress load management has a cost, called “allostatic load”. Under repeated stress, the physiological changes become less “elastic” and more and more difficult to reverse; are adaptive and healthy responses in the short term [471], that may have negative consequences in the long term [472]. From this perspective, there is nothing “broken” or “sick” in the molecular PNEI regulation mechanisms, nor are present aberrations of cellular signaling pathways: simply, the brain, persistently alerted by environmental stimuli that considers as threats, performs nothing more than his job, keeping the physiological parameters at the set-point that believes (and has learned through experience) most suitable to deal with a threat, real or perceived that is [473,474].

Going back to the blood pressure example: over time a thickening of the muscle layer of the arterioles occurs and even if we restore a state of maximum relaxation, blood pressure does not return to values of “normality” because of the need to push blood against an increased resistance (with potentially very harmful long term consequences on heart and vessels). Of course, the allostatic burden can show different aspects: can be linked to the excessive production of mediators of stress, some of which are toxic at high concentrations (the chronic presence of excessive levels of cortisol damages the hippocampus neurons and inhibits neurogenesis, hindering neuroplasticity, learning, memory and future further adaptations [475-478]); immune suppression can occur, with greater tendency to infections or predisposition to cancer [479,480]. The concept of allostatic load makes us see how fundamental our behavior and our way of life are to maintain health. As we will see, our behaviors obviously affect health, some positively, as a good sleep, a proper and prudent diet or moderate physical exercise and other negatively as smoking, the use of alcohol or drugs. The individual behavior can in turn increase or decrease the allostatic load, modulating the network of molecular PNEI relations.

Mental or physical stress lead to PNEI and epigenetic alterations with significant consequences, chronically or acutely. Another example concerns the modulation of endothelial function as a prelude to many CVD.

plasticity and learning process [146-149], for the immune system following an infection, a mental stress or exercise [150,151,152] and so on. Thus, after any experience that changes the PNEI network, it does not return to the origin point ("homeostasis") but always to another balance ("allostasis"). This process have been studied scientifically by McEwen *et al.*: *"the mind involves the whole body and two-way communication between the brain and the cardiovascular, immune, and other systems via neural and endocrine mechanisms. Stress is a condition of the mind-body interaction, and a factor in the expression of disease that differs among individuals. It is not just the dramatic stressful events that exact their toll, but rather the many events of daily life that elevate and sustain activities of physiological systems and cause sleep deprivation, overeating, and other health-damaging behaviors, producing the feeling of being "stressed out." Over time, this results in wear and tear on the body which is called "allostatic load," and it reflects not only the impact of life experiences but also of genetic load, individual lifestyle habits reflecting items such as diet, exercise, and substance abuse, and developmental experiences that set life-long patterns of behavior and physiological reactivity. Hormones associated with stress and allostatic load protect the body in the short run and promote adaptation by the process known as allostasis, but in the long run allostatic load causes changes in the body that can lead to disease. The brain is the key organ of stress, allostasis, and allostatic load, because it determines what is threatening and therefore stressful, and also determines the physiological and behavioral responses [153]. Brain regions such as the hippocampus, amygdala, and prefrontal cortex respond to acute and chronic stress by undergoing structural remodeling, which alters behavioral and physiological responses [154]. Translational studies in humans with structural and functional imaging reveal smaller hippocampal volume in stress-related conditions, such as mild cognitive impairment in aging and prolonged major depressive illness, as well as in individuals with low self-esteem. Alterations in amygdala and prefrontal cortex are also reported. Besides pharmaceuticals, approaches to alleviate chronic stress and reduce allostatic load and the incidence of diseases of modern life include lifestyle change, and policies of government and business that would improve the ability of individuals to reduce their own chronic stress burden"* [145].

This is important not only for every single person, because we have already seen that allostatic load will pass from generation to generation, through epigenetic markings.

This process makes clear the inheritance of cardiovascular diseases, such as combination of genetic stress expression programming/vulnerability to stress and environmental factors. And is easily understand the mechanism by which the populations of immigrants from suburban areas or from the countries of the southern hemisphere, with lower cardiovascular risk [155,156], acquire the same or even higher cardiovascular risk of the territory in which they arrive [157,158].

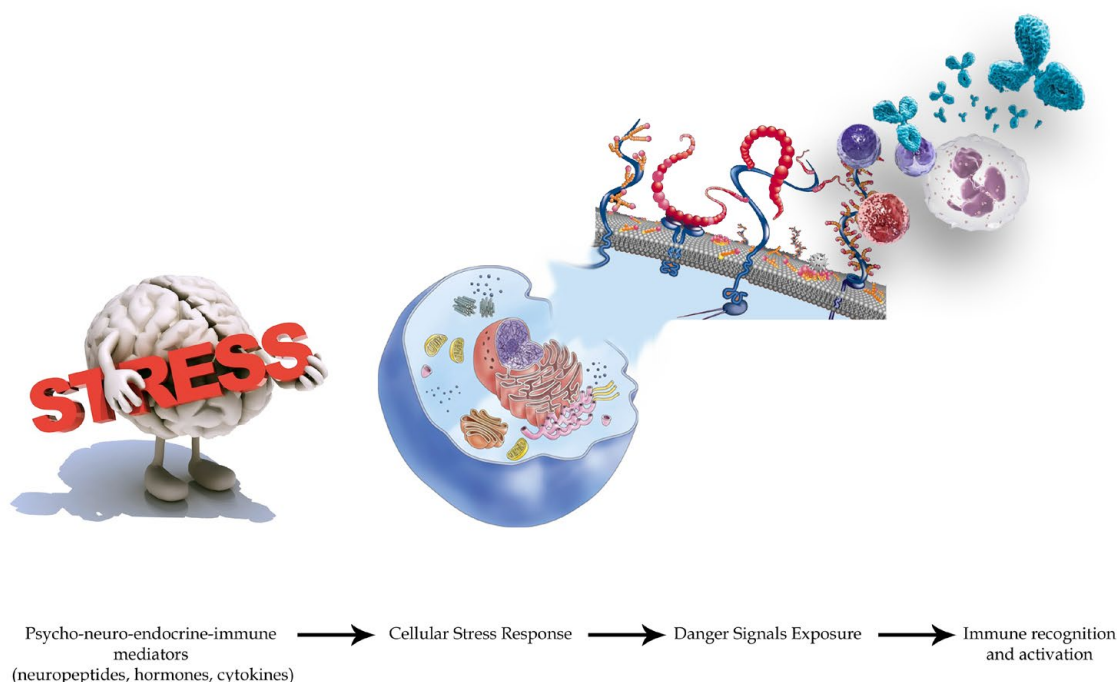
The stress response involves three stages: an alarm phase, a phase of resistance and the final stage of exhaustion [159]. By this concept and the concept of allostatic load, it follows that the process leading to what we call "disease" is something slow, chronic, often not symptomatic, which provides a remarkable ability to compensation by the body, until exhaustion and the onset of acute symptoms or severe and life-threatening conditions. A typical example is the case of endothelial function. We have seen that endothelial cells are the target of hundreds of molecules that are activated under stress. The condition of chronic endothelial stress triggers the process of atherosclerosis until myocardial infarction [160].

## The long lag phase and compensation. What happens in the single cell under stress? The universal cell reaction

Heart rate and cardiac output vary in response to the needs of the body's cells for oxygen and nutrients under varying physical and psychologic conditions. In order to respond rapidly to the changing requirements of the body's tissues, the heart rate, contractility and perfusion are regulated mainly by the nervous system, hormones, immune and intrinsic factors [161].

Let's see what happens in a single cell in a condition of stress (Figure 3). We present below only some key mechanisms. Our goal is not to go into the very complicated genetic and intracellular signaling pathways, but is to understand some of the principles of cell's behavior under stress. Different cells then, may present slightly different behaviors depending on their type and the organ to which they belong, but these mechanisms are fairly shared.

The body is made of cells and the same comments that we made for the macroorganism are shared by the cellular world. The "universal cell reaction", a coordinated biphasic response to external (noxious and other) stimuli observed in all living cells, was described by Nasonov and his colleagues in the mid-20<sup>th</sup> century [162]. Even at cellular level, after a stress, a phase of alarm follows, an adaptation stage and exhaustion through apoptosis or cell death in the event of continuous overload condition. Cells typically respond quickly to stress, altering their metabolism to compensate [163]. Various signals from the outside, often converge on same intracellular effectors making an intricate modulation game of cellular response. An interesting example of this concept, as yet largely unknown, is represented by the proteins Shc (Src homology and collagen omology) whose action spans several systems including the intracellular cascade of many G protein-coupled receptors and tyrosine kinases receptors such as Ras/MPKP (mitogen activated protein kinase) and IP3 (phosphatidylinositol 3-kinase)/Akt, integrins and cytosolic kinases, cytokines [164]. Shc proteins play a key role in the cellular response to stress [164]. A cell will tend to activate and optimize all metabolic processes designed to maintain or even maximize the production of energy [165] (for example, through Sir2-alpha-p53 axis) [166]; will seek to maintain its own shape, dimensions [167,168] and polarity (through LKB1-AMPK signalling system) [169]; the stress sensors protein kinase RNA-like endoplasmatic reticulum kinase (PERK), inositol-requiring protein 1α (IRE1α) and activating transcription factor 6 (ATF6) stimulate a homeostatic signalling network called "unfolded protein response" (UPR) that orchestrates the endoplasmatic reticulum's function in order to preserve cell function or at least its integrity in case of excessive stress [170-172]; moreover, the stressed cell regulates the processes of DNA transcription and replication by inhibiting the synthesis of proteins unnecessary to overcome the acute event, saving energy and diverting its inherent resources in those activities aimed at promoting the survival of the cell [173] (heat shock proteins' (Hsp) response, UPR response, DNA damage response, PPAR etc [174-176]). If the stress stimulus persists, the cell switches from prosurvival signaling to signaling systems that will lead to apoptosis or death [177,178]. Stress modulates the rate of cellular aging. Epel *et al.* provided the evidence that psychological stress--both perceived stress and chronicity of stress--is significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length, which are known determinants of cell senescence, promoting earlier onset of age-related diseases [179]. Furthermore, mitochondria contribute to immune activation following cellular damage and stress, generating reactive oxygen species (ROS) [180,181]. In normal conditions, the oxygen radicals produced by the



**Figure 3.** Psychological stress alone is able to trigger oxidative stress and the universal Cellular Danger Response (CDR). Moreover, in the CDR context, an extracellular matrix remodeling happens with the exposure of certain “danger-proteins” (danger associated molecular patterns or “DAMPs”, matrix metalloproteinases or “MMPs” and high mobility box 1 or HMGB1) and fibrosis that can boost further the immune response. Furthermore, pro-angiogenetic substances are secreted with the goal of recruiting more energetic resources. All these phenomena involve epigenetic modifications by the action of circulating micro RNAs. We want to focus on the importance of the neuro-endocrine-immunitary impact of chronic stress (physical and mental) for health and cardiovascular balance. In particular, among the mechanisms described, we want to emphasize as a situation of prolonged psychological stress is inscribed in the extracellular matrix through some major mediators such as beta2 adrenergic receptors-protein kinase A, vascular endothelial growth factor (VEGF), MMP-2 and 9, S100A1-9, DAMPs (heat shock protein-72, HMGB1, proteins RAE-1 and Multi1). These elements are the “warning signs” recognized by the immune system (through TLR-4 pathway). Studies performed on biological tissue scaffolds by Daly *et al.*, demonstrated that these elements are able, alone, to evoke an inflammatory response when implanted in vivo [481]. All these aspects take on very intriguing contours and nuances if we consider the evidences that link in a double-locked way the psychological/emotional profile of a subject with the phenomenon of inflammation and harmful effects, with tissue damage, at cardiac level [482].

mitochondrial metabolism are critical to modulate a number of kinases and phosphatases, redox sensitive transcription factors and genes [182,183]. In this context the NO plays a central role [184]. Under conditions of stress, and continuous demand for energy surplus [185], ROS could become excessive, creating a toxic environment within the cell (ROS damage mitochondria, cell membranes, DNA, proteins, and lipids), that will affect its survivor [186]. Naviaux *et al.* demonstrated that ROS and chronic oxidative changes in membrane lipids and proteins found in many chronic diseases are not the result of accidental damage but are the result of a highly evolved, stereotyped, and protein-catalyzed “oxidative shielding” response that all eukaryotes adopt when placed in a chemically or microbially hostile environment [187]. Thus, ROS production and the condition of “oxidative stress” is the response to a chronic metabolic condition of stress acting on a cell, not the cause [187,188].

The continuous functional cellular overload [185,189], is signaled to the immune system, which in turn will be constantly activated, creating a condition of low-grade chronic inflammation [190].

A new paradigm in immunology reveals that the driving force for the immune system is the need to recognize danger, not only “self” or “non-self”. The model starts with the idea that the immune system defines “danger” as anything that causes tissue stress or destruction. In this model, antigen-presenting cells are activated by alarm signals

from stressed or damaged tissues. Without this activation, no primary immune response can occur [191]. As a matter of fact, Gallucci *et al.* demonstrated that dendritic cells, the most potent antigen-presenting cells, need to be activated before they can function to initiate an immune response. In the absence of foreign substances, dendritic cells can be activated by endogenous signals received from cells that are stressed, virally infected or killed necrotically, but not by healthy cells or those dying apoptotically [192].

In this way, during the cellular response to stress (cell danger response (CDR), the cell continues to signal to the immune system its dangerous condition, activating a sterile inflammation (or inflammasome [193,194]). The innate immune system can sense danger signals through different pathogen recognition receptors (PRR) such as TLR, nod-like receptors and receptors for advanced glycation endproducts and the activation of a PRR results in the production of cytokines and the recruitment of leukocytes to the site of injury [195].

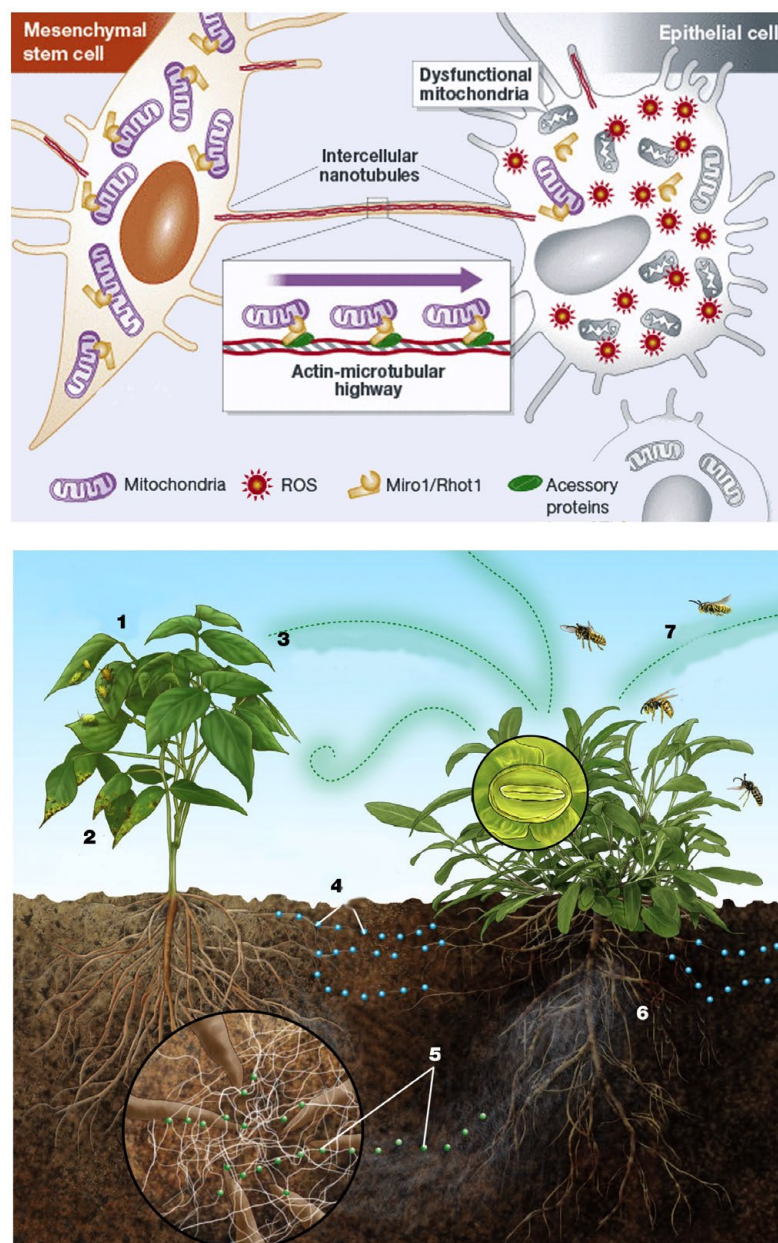
After the danger has been eliminated or neutralized, a choreographed sequence of anti-inflammatory and regenerative pathways is activated to reverse the CDR and to heal [193]. When the CDR persists abnormally, whole body metabolism and the gut microbiome are disturbed [196], the collective performance of multiple organ systems is impaired, behavior is changed [197,198], and chronic disease results, through PNEI network activation (allostatic load)



[199]. It is interesting to note that psychological stress alone is able to trigger the CDR [200].

Moreover, in the CDR context, an extracellular matrix remodeling happens [201-205] with the exposure of certain “danger-proteins” [195,206] (danger associated molecular patterns or “DAMPs”, matrix metalloproteinases or “MMPs” and high mobility box 1 or HMGB1) and fibrosis [195,206-214] that can boost further the immune response [215-218]. Furthermore, pro-angiogenic substances are secreted with the goal of recruiting more energetic resources [189,219-222]. All these phenomena involve epigenetic modifications by the action of circulating miRNAs [223]. Finally, it was recently discovered that a cells under stress strengthens their ties with neighboring cells

through connections called “tunneling-nanotubes” or TNTs, through p53 activation [224]. TNTs represent a subset of F-actin-based transient tubular connections that allow direct communication even between distant cells [225]. These structures have been found in numerous cell types and shown to transfer electrical signals and cytosolic materials such as ions, nutrients, proteins, organelles, plasma membrane components and miRNAs [224-232]. This type of structures are also present in plant and animal cells [233]. It's wonderful to note that even the same stress response, both on the body and on the cellular level, it is similar to what happens in nature in the plant world. Even the plants in a forest make connections between them to respond to dangers [234-236]. The Figure 4 shows the comparison with the plant world.



**Figure 4.** An endothelial cell in danger (under stress) reports its condition to the surrounding cells secreting various substances (see main text), and creating connections with them, called tunneling-nanotubes (TNT). Similarly, when insects or viruses attack a plant (1 and 2), the plants attacked emit signals in the air (3) and in the soil (4). These latter signals, passing through a network of fungi that connects the roots of the plants between them (5), alert neighboring plants, that, in turn, attract predators of insects that are attacking the plant in difficulty (7). Modified from [483] and [484].



In conclusion, it is currently understood that the cellular stress response is a hallmark of many common human diseases: firstly, because the stress stimulus may be too strong and/or prolonged, thereby allowing insufficient time for recovery to the normal status and secondly, a stressed cell's ability to handle even physiological levels of stress load may be altered in disease states, similarly resulting in detrimental outcomes [174]. An understanding of the CDR permits us to reframe old concepts of pathogenesis for a broad array of chronic, developmental, autoimmune, and degenerative disorders (including autism spectrum disorders, attention deficit hyperactivity disorder, asthma, atopy, gluten and many other food and chemical sensitivity syndromes, emphysema, Tourette's syndrome, bipolar disorder, schizophrenia, post-traumatic stress disorder, chronic traumatic encephalopathy, traumatic brain injury, epilepsy, suicidal ideation, organ transplant biology, diabetes, kidney, liver, and heart disease, cancer, Alzheimer and Parkinson disease, and autoimmune disorders like lupus, rheumatoid arthritis, multiple sclerosis, and primary sclerosing cholangitis) [199,237].

Exposure to stressful stimuli, such as psychological stress, activates HPA axis inducing cellular oxidative stress [238-240]. As the doctrine of the PNEI network teaches, all physiologic processes are doublelocked: for example depression causes oxidative stress and it is even true that the condition of oxidative stress can cause depression [30,241].

The activation mode and the extent of neuroendocrine responses depends on the type of stimulus and can, as we have seen, be partly inherited [138,242,243]. The stress response is non-specific and unambiguous both in body and in individual cells that compose it.

It's easy to understand how the continuous action of a physical stress, by acting continuously on a point or on a specific organ of our body, can determine, over time, its dysfunction linked to the processes described up to here. The future challenge will be to understand how, in the same way, each type of mental stresses are written into our bodies, maybe hitting particular organs; or how, after determining a generalized response, lead to the onset of organ dysfunction and symptoms, simply in the more "epigenetically vulnerable" district.

## The atomic world: life is a symphony of oscillatory patterns

### Biological rhythms

All life on Earth is based on the alternation of cyclical phenomena, which can describe a precise rhythm, a definite oscillation/vibration. There is a day/night cycle, the seasons, solar/moon cycles, heart beats and breathing activity, the oscillation of the electro-magnetic fields and atoms. All observable phenomena encompass a symphony of precise rhythms. Many human biological responses are orchestrated and integrated within these cycles [244], and many of the behaviors and physiology of the animals and humans are related to the lunar phases [245]. Human society is structured around the lunar rhythm [246,247], even playing its influence regardless of our awareness of the current moon phase [248]. All our lives contain an infinite number of rhythms, with vibrations that move from atomic to molecular floor and biochemical metabolic reactions. Fluctuations in our brain activity, heart and respiratory rates correlate with our emotions, thoughts and our psycho-spiritual attitude [249,250]. Many common diseases in humans (such as cancer, heart disease, diabetes mellitus or psychiatric disorders, such as depression) seem to be linked to disruptions of circadian cycles and to clock genes variation [251]. In this way, rhythms communicate bioinformation that governs a wide variety of functions,

including guiding that of living beings towards health and well-being [252]. In fact, pulsatile dynamics provide critical capabilities to cells in stress response, signaling, and development [253].

All living processes are based on the timing of a myriad of rhythmic phenomena and the brain plays a key role in directing this symphony. It has been seen that the central nervous system acts as a center of fusion and integration of different cellular and subcellular oscillatory signals. For example, it has been shown that the regulation of metabolism and energy production of the entire organism across the daily cycles of fasting and feeding is orchestrated by subcellular transcriptional oscillations (clocks) controlling the basic dynamics of substrate biosynthesis and energy production (adenosine triphosphate, ATP) at the mitochondria [254]. Then, let's think to the development of an embryo, the neuronal plasticity and to the phenomena connected with the memory process, to the differentiation of stem cells and the biological response to stress: everything is based on the rhythmic activation of genetic sequences called "clock genes" [251,255-257].

All the just mentioned processes, as well as the heart and vascular myocells' contraction, are regulated by the  $\text{Ca}^{2+}$  ion and there are processes able to adjust with precision its availability in the cytosol. In particular, it has recently been described cellular pacemakers sites generating subcellular  $\text{Ca}^{2+}$  waves and oscillations, to regulate the condition of myocellular contraction [258]. Nature choses to create subcellular clocks to guarantee an exquisite regulation of the  $\text{Ca}^{2+}$  dynamics essential for many processes.

In general, aberrant cellular oscillatory patterning is associated with severe diseases, ranging from primary ciliary dyskinesia (loss of molecular motors that power ciliary beating, abnormal lung development and function, infertility, situs inversus and severe heart malformations [259,260], to metabolic syndrome [261] or cognitive disorders [262].

Underlying all of the above reported findings one may see that the coupling of intrinsic oscillatory rhythms originating at the molecular and single cell level is intimately related to higher-level structure, function, and the generation of a wide range of biological rhythms [263]. At the cellular and subcellular levels, oscillatory behaviors have been shown to emerge as a direct result of simple negative feedback loops and coupled positive and negative feedback loops [264], and rhythms arise from stochastic, nonlinear biological mechanisms interacting with a fluctuating environment [265], indicating that oscillations are a natural outcome of a variety of essential cellular biochemical interactions. Another concept central to the study of biological rhythms is the existence of coupling between oscillators giving rise to collective behaviors such as phase synchronization [265]. For example, this is a modern key concept of the neural network functioning [266-268] and it's important to understand common synchronous cellular behaviors in spite of intrinsic parameter fluctuations and the presence of extrinsic noise [263] or the recently discovered "chimera states" in networks of coupled oscillators wherein a wide spectrum of complex states emerge from the underlying dynamics of a system of weakly coupled oscillators containing both synchronous and asynchronous elements [269]. Thus, the progression toward rhythmicity and complex behavior is a natural outcome of multipart, dynamically interlinked systems.

### Cell-cell communication and endogenous Electro Magnetic Fields (EMF)

We are constantly immersed in both natural and human-made EMF. In particular, life on earth has evolved under the influence of its

geomagnetism. The earth produces weak EMF of about 50 microTesla [263]. Nowadays, the effect of these constant magnetic currents of extremely low frequency (ELF) on biological systems and in particular in humans, have been clearly demonstrated [270,271]. In addition to a significant amount of literature on bioeffects due to geomagnetic-range field strengths, a growing body of evidence has shown that effects can also occur at much lower field strengths (on the order of nanoTesla) showing that the energies of interaction are substantially lower than the average random thermal energy due to Brownian motion [271], suggesting the existence of a more subtle level of bioinformation transduction operating at extremely low energies.

Muehsam *et al.* brilliantly summed up, in a recent review [263], many examples related to the biological and molecular effects of EMF and solar influence on the biological balance of the earth.

From what we have seen so far, each atom in our body is made and is embedded within an interconnected network of oscillatory elements. For example, adenosine receptors are being studying as molecular vibrating structures, communicating through fluctuations [272]. Every harmonic oscillators interact with one another creating living aggregates, cross-talking with each other and with the environment, transforming inner and outer stimuli into electromagnetic and chemical signals [273]. The inter-atomic synchronization, with resonating rhythms, determines their functional assembly into molecules, cells, tissues, organs, and entire individuals [274,275].

From this point of view, intercellular communication is critical for normal physiological processes, so much that we can consider diseases as simple changes in communication between cells [276], under the PNEI macro-system described. In fact, defects in cell-cell communication are associated with a wide variety of diseases, including diabetes, autoimmune disorders, atherosclerosis, cancer, neuropathy, and infertility, among others [277].

Due to the oscillatory nature of the elements that compose it, also the communication between the cells occurs by means of EMF which are able to activate of membrane proteins, and specifically proteins involved in signal transduction mechanisms [278].

Once again, a key example is related to NO and the influences it receives from EMF. According to Muehsam *et al.* [263]: “*NO diffuses freely and rapidly across cell membranes, plays key roles in the rapid regulation of microcirculation, inflammation, and the cell growth and repair process [279], and has been demonstrated to regulate chromatin folding dynamics, and thus gene expression, in human endothelial cells[280]. The importance of transient NO signaling is underscored by the observation that Nature has evolved a remarkable sensitivity to subcellular, subsecond (100 ms) NO transients in the low picomolar range, as demonstrated in human embryonic kidney HEK 293T cell lines [281]. A growing body of literature has demonstrated that NO signaling plays a significant role in biological EMF transduction, and effects on NO expression and NO-dependent pathways have been reported for a wide variety of nonthermal EMF amplitudes, frequencies, and signal shapes [282-289]. Thus, modulation of NO signaling has been established as one means by which cells and tissues can respond rapidly to changes in the EMF environment and could interact with nuclear DNA through modulation of chromosome folding dynamics [280]*”.

From what has been said so far, we can understand the recent alarming observations by Lancellotti *et al.*, about the negative effects related to cardiac magnetic resonance that was found to be associated with minor but significant alterations or immediate blood cell

activations figuring inflammatory response, as well as DNA damage in T lymphocytes [290].

### **In summary: Physics crumbs to interpret a human being [263,291]**

Using the sight provided by Physics, the web of life can be seen as a complex system made of matter and the ultra-structure of matter can be understood in terms of harmonic oscillators, or tiny subparticles in constant vibration (please see the video: “Powers of ten © 1977 EAMES Office LLC, available at [www.eamesoffice.com](http://www.eamesoffice.com) or at <https://www.youtube.com/watch?v=0fKBhvDjuy0>). All reality is quantum energy in terms of vibrations according to specific information (frequency, wave length, harmonics etc.).

These harmonic oscillators interact with one another creating living aggregates, cross-talking with each other and with the environment, transforming inner and outer stimuli into electromagnetic and chemical signals.

This signal transmission allows the dynamic balance of the living system with itself and with the surrounding environment. Intra-matter dialogue occurs in terms of resonance (oscillating tendency), coherence (fixed relationship between the phase of interacting energy waves) and complexity. Simply stated, everything at a subatomic level is in dynamic oscillation and interacts with other oscillating elements. The system tends to assume an oscillating modality that is the sum of its components. It can be described by depicting its oscillation characteristics (frequency, wave length, energy etc.), its coherence (the relationship between the phase of its components) and according to its complexity (the number of elements that build it, its inner relationship, environmental influences and so on).

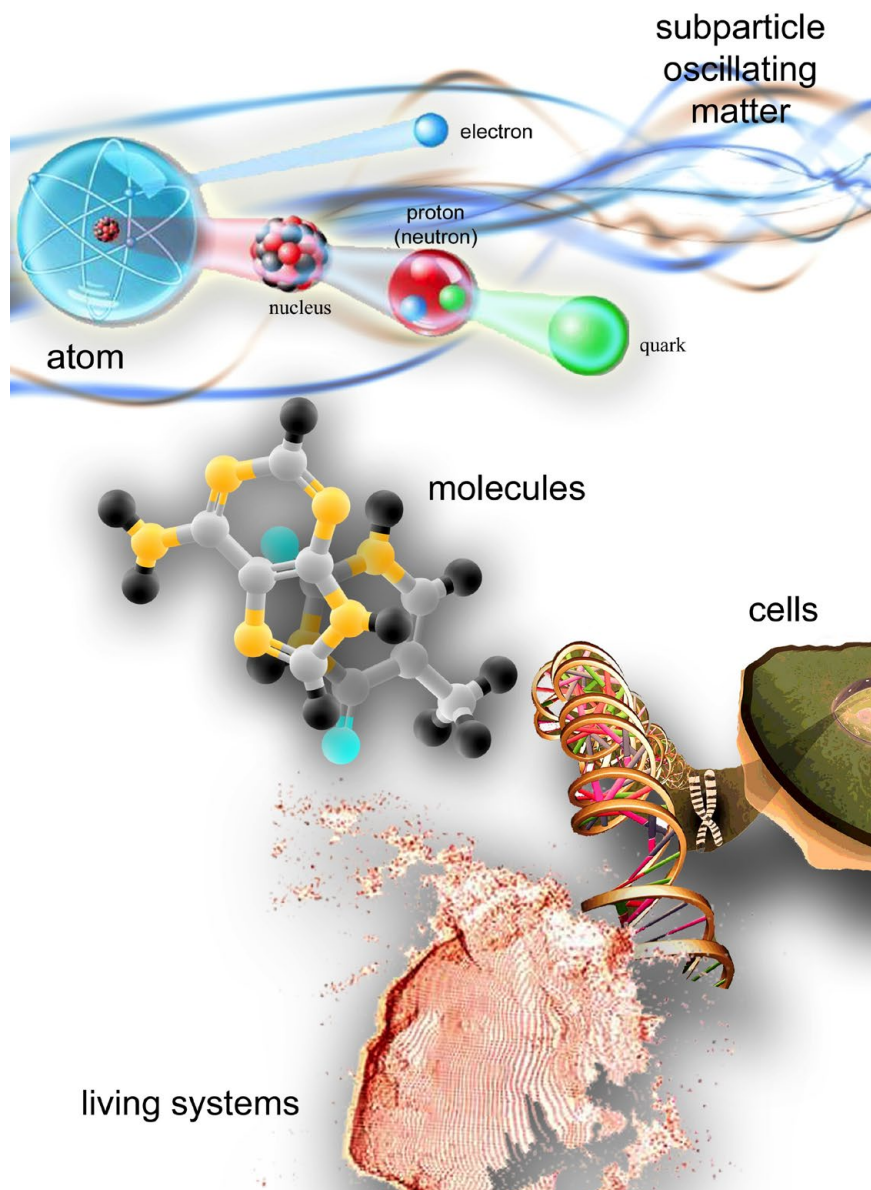
Brian Greene, professor of Physics at the Cornell and Columbia University is a proponent of the “superstring theory” with which science is describing the vibratory nature of creation. According to this theory, which unifies Einstein’s theory of relativity with Planck’s quantum mechanics, the microscopic world is full of tiny violin strings (long about a hundred billion of billion less than an atomic nucleus) which, according to their vibrational conformation, give rise to the different atomic structures (quarks, neutrinos, electrons etc.) [292]. At the microscopic level, the universe is a symphony of sounds that give rise to all matter [293].

Different works describe neural and genetic network activity from this point of view [294].

In other words, only particular proportions in the subparticles’ oscillation pattern allow their tuning and their aggregation into atoms, molecules and more complex systems (Figure 5).

Thus, every single person could be depicted as a complex system of resonating matter in which some particular notes can be recognized, or some frequencies with which its atoms and the molecules of life are constantly assembled and renewed: (1) heart rhythm: 40-80 beats per minute, 0.666-1.333 Hz; (2) breathing: 15-24 breaths per minute, 0.25-0.4 Hz; (3) platelet lifetime: 7-10 days,  $1.66 \times 10^{-5}$ - $1.25 \times 10^{-7}$  Hz; (4) oscillating frequencies of Sodium or Potassium ions: 43 and 47 Hz; (5) brain waves: epsilon 0.5-1 Hz, supradelta 1-2 Hz, delta 2-4 Hz, theta 4-8 Hz, alpha 8-16 Hz, beta 16-32 Hz, gamma 32-64 Hz, supergamma 64-128 Hz [294].

The correct and healthy function of our body, from an atomic point of view, seems to be like a big, harmonic musical symphony with particular proportions and relationships (and we currently handle it



**Figure 5.** Matter is composed by oscillating elements. The oscillation pattern of subparticles allows them to tune and aggregate into atoms, then into molecules, cells, tissues and more complex living systems. From this point of view, we are vibration, we are like music. We can speculate that music, composed with certain proportions between notes, interacting with subatomic matter, makes up the harmony in its swing, restoring a “healthy balance” at macroscopic level. The effects of music on health are independent from the type of music and from the subject’s taste. It is also conceivable that the same happens with thoughts and feelings, which may correspond to different oscillatory patterns at subatomic level. We constantly vibrate according to love or according to fear, influencing our surroundings and being affected by them. As the saying goes: “as we love ourselves we love others and our surroundings”.

with our diagnostic tools, such as magnetic resonance imaging, X-ray methods or ultrasounds).

### **The need for new theoretical models and new perspectives in medicine and life sciences, in order to understand and cure the human being**

In our long journey in the understanding of endothelial function we dug deep, from the plane of the human being understood as a macrocosm of PNEI-connections, down to the cellular, the molecular and atomic floor. The whole structure of reality is an interconnected

network of elements, in constant dialogue. The example of the endothelial function and its determinants, emphasizes the need for new theoretical models and new perspectives in order to understand and cure the human being.

### **The need to reduce the distance between medicine and its theoretical foundation: the physics**

Contemporary physics, thanks to the theory of relativity and quantum mechanics, is flocking to the study of systems far from the equilibrium concept and to the study of the laws of chaos. This



approach puts in crisis the Western medical model, which is still based on the mechanistic Newtonian paradigm. Instead of a linear view of reality, based on the cause-effect relationship, it emerges a circular structure, where each element is always in relation to the complexity: each element affects and is affected by the complexity that surrounds it [295]. It's clear that this new scientific perspective hits a biomedical model based on a mechanistic and reductionist vision of human pathophysiology and based on a sectorialized and hyper-specialistic clinical point of view.

Since the early days of quantum physics, its influence on biology has always been present in a reductionist sense: quantum physics and electrodynamics shape all molecules and thus determine molecular recognition, the workings of proteins, and DNA [296]. Also van der Waals forces, discrete molecular orbitals, and the stability of matter: all this is quantum physics and a natural basis for life and everything we see [297].

As West pointed out [298], *"as scientists we measure things; the position of stars in the sky, the sounds of the stars [299], the amount of rainfall in a region over the year, the precise pathway of water movement from the soil through the plant roots [300], tidal networks [301,302], or the number of heart beats per minute of a patient in our care. These numbers tell us about the phenomena we want to understand. An astronomer deduces whether the faint dot over head is a fixed star, a moving planet or a rocketing comet using the physical theories of cosmology. The numbers tell the meteorologist if there is a pattern of increasing or decreasing rainfall and whether that pattern indicates an organized change in the weather. A physician determines whether the pattern in the heart beats reveals if the patient has a cardiovascular problem that requires intervention or s/he is having an anxiety attack. Each science organizes measurements in ways that communicate the most to the practitioner and taken as a group they constitute the scientific view of the world, which is to say that if it is a matter of science it can be measured. In keeping with the data-based perspective, the measurements in and theories of molecular biology and genetics in the latter half of the twentieth century produced a shift in medical outlook from the pathologies of the cardiovascular, respiratory and motor control networks to the influence of molecules on health and well being. However, in the past decade or so the pendulum has begun to swing back from the concentration on individual molecules to a focus on the properties of networks of molecules and a determination of the emergent properties of such complex interactive networks. This is particularly true in physiological networks, which exhibit complex, non-stationary, intermittent, scale-invariant and non-linear [303] behavior [304]"*. New mathematical models are then emerging to explain the matter and pathophysiological phenomena. The complexity and interdependence of reality put in check the concept of linear cause and effect.

A system is a collection of interacting elements. Behavior of the system is distinct from the behavior of its parts or elements. These elements interact with each other directly and indirectly to modulate the system function. The reductionist or mechanistic view of nature involves reducing systems into their component parts (elements) in an attempt to understand them [305]. This is the basis of linear system analysis, where output is proportional to or can be determined through applying simple differential equations to the input. Yet systems within nature, including the human body, frequently lack mechanical periodicity or linear dynamics and thus are referred to as nonlinear systems [306]. Within nonlinear systems, output is usually not proportional to input, and output for the same input value may not be constant over time [307]. Furthermore, in contrast to linear systems, breaking a nonlinear

system down into its elements (parts) and analyzing those parts under controlled conditions does not accurately reflect the complex behavior present, nor capture the dynamic relationships operating between various elements [308,309].

The so-called "network effect" (and endothelial function is a good example of this) is being investigated through the fractal statistics [298], chaos theory [310-314], systems biology [315-319], Heisenberg S-Matrix and Feynman Diagrams [320], Nash equilibria [321-326], Steiner trees [327,328], distribution-free approach to constructing the confidence region of multiple parameters [329].

The approach to construct confidence intervals for the study of individual parameters or to develop confidence regions for two or more parameters, requires that the distribution of the estimated parameters is known or can be measured. Actually, the sampling distributions of parameters of biological importance are often unknown or difficult to be characterized. From what it has been described about the influences playing on endothelial function, it is easy to understand how it cannot exist a standard CFR value of reference common to all people, because simply varies rapidly from person to person and even in the same individual, depending on his state of psycho-social or physical stress, on his emotions, alimentation etc. From the network point of view, no biological parameter measured in clinical practice can be separated from the other. As an example, plasmatic cholesterol and troponin vary their own levels after a simple mental stress [43,330-333], or inflammation parameters and fibrinogen vary with emotions of happiness or sadness [334]. Given the individual variance, is very superficial perform clinical studies to measure risk thresholds (that will become clinical guidelines) [48] without taking into account the psychological characteristics of the population studied, assuming that these elements vary depending only with physical activity, alimentation and a set of gene activation that is fix and unchangeable. By the vision described up to here, it's not strange to notice that those who want to assess hypothetical risk thresholds do not take into account these concepts and states, for example, not being able to explain the pathophysiological reasons for the release of low doses of troponin from some patients [335]. They simply ignore completely the perspective of the network, in favor of a simplistic, mechanistic and reductionist mentality, that simply not longer holds standing.

Actually, as has been clearly explained McCormack *et al.* [336], researchers can look at very similar data yet having completely different conclusions based purely on an over-reliance of statistical significance and an unclear understanding of confidence intervals. According to the authors, observations and results should speak for themselves, without the need for interpretations, and even if a threshold seems reasonable, it can never be used to make dichotomous conclusions. [336] Clinicians have not to use trials like drunks do with street lamps: not to light but to lean against, even if the author is a scientist of fame [337]. Moreover, Giannoni *et al.* demonstrated that in nature and in human beings there is no kind of threshold and well explained how common clinical research procedures routinely produce false thresholds [338].

These considerations will be fundamental in the study of the PNEI-cellular-molecular network dynamics that affect endothelial function and its evaluation, for example, by CFR. Furthermore, from all these observations, remains crucial in an impressive and overbearing manner the way all of us look at the reality. With statistics, while remaining an important and fundamental analysis tool, everyone can deny the obvious depending on how the reality is observed (Figure 6). For example, we must always remember that we are exploring a reality



**Figure 6.** Gestalt discipline tries to understand the laws by which we structure our perceptions. The perception of reality does not depend from the elements, but by the structuring of the elements. Thus, what we see is equivalent to how we see it and it is conditioned by past experiences. In this design, you recognize a young woman or an old lady? Then, depending on our point of view we use the statistics to describe the phenomenal associations observed. It must always be remembered, however, that showing associations between phenomena is not enough: it is essential to track a biological plausibility, a mechanism, in what is observed.

in which is already acting individual stress and that of generations before. What we consider “normal” might already be stressed out and so should not be taken as a reference point, a goal or as “objective”.

### Considerations about the epigenetic regulation of the genome

All cells in the body contain the same genome, but achieve their specific identity, through specific programs of gene expression. The way in which each cell type interprets genomic information is closely linked to the organization of DNA regulatory elements [339]. The Mendelian idea of the gene as a unit, the interpretation of genes as structural and/or functional units in the genome is challenged by evidence showing the complexity and diversity of genomic organization [340,341].

Many disorders do not occur suddenly but are the result of a long process of adaptation involving psychological, nervous, endocrine and immune factors (as in case of endothelial function, atherosclerosis and myocardial infarction) [342-345]. Cytokines, hormones and neurotransmitters act every moment of our life regulating the expression of our genes and creating patterns of activation that can be transmitted to future generations [346] as a sort of “cellular memories”, related to epigenetic signatures [347,348].

Nowadays, geneticists say that some “classical genetic diseases or predisposition” can be connected to an alteration in the expression balance of genes [349,350], rather than the presence of a gene considered “sick”, being the evidence that even many Mendelian diseases, cannot be explained by simple genotype-phenotype relationships [351,352].

In addition, also many cardiological pathologies are now related to an anomaly in the folding of proteins [353] at a post-transcriptional level in relation to the REDOX state of cardiac cells [354]. We have already seen how this state can be influenced by emotional distress.

Thus, from the point of view of epigenetic inheritance, many diseases could be interpreted as generational inheritance of adaptations to the environment and its various forms of stress.

Remaining in the perspective of the central dogma of DNA, who knows how many “genetic abnormalities” and “defective” proteins are present in people phenotypically normal and healthy; we do not know them because we do not see and study them, simply because those people have epigenetic balances that do not run into that state we call “disease”.

Then, it makes sense to talk of “disharmony”, of a “disease”, nothing other than linking it to a specific external and internal environment (physical and psycho-social). The problem is not so much the presence of a single “sick” gene and its product, but its expression. It’s obvious that, removing the gene from the DNA (Knock-out experiments), we won’t look more a certain phenotype [355], but is not the only solution, and especially is not the way in which it seems to work the genome, which instead aims to regulate its expression in function of the environment. A gene can be silenced. The knock-out studies only show an association between the presence of a gene and its products and a pathology, but the setting of a precise genetic network is very wide, “often lie outside expected pathways” [341,356], and cannot be neglected.

In fact, as we will see, it is possible to change the cellular memories (related to our lives or transmitted by previous generations) acting on behaviors, nutrition and our emotions, taking advantage of the responses of the immune system [357].

Moreover, the single molecule of DNA responds to the environment: going down again in the molecular/atomic plane, our genes possess particular vibrational frequencies of resonance [358-361]. In particular, according to recent discoveries of molecular quantum physics, the DNA can be understood as the result of electromagnetic waves (in resonance with the cellular and macroscopic environment) that enable communication between cells [362,363]. Given the vibratory nature of DNA, researchers are studying the ways in which the genome is expressed, using special sounds [364-369].

In summary, a music consists of melody and harmony. By comparison with music: the genes are like the melody track; epigenetics is the harmony, the way of melody expression, that can “change music” even if the melody remains the same (please, to have an idea of this concept, listen to: 12 Variations on “Ah, vous tell-je, maman”, KV265 (1778) WA Mozart (1756 - 1791), and watch: Nature video” Epigenome: The symphony in your cells”, <https://www.youtube.com/watch?v=W3Kg9w-srFk>).

Thus, Epigenetics brought a big change of view in Biology and Medicine. In particular, it has been shown that some phenotypic changes, marked by methyl-signs on the genome, can be transmitted to the next generation [370]. Thanks to epigenetic evidences, has changed

the scientific model applied in the field of classical genetics: may no longer exist the “gene-centrism” and so also the mechanistic and reductionist model of biology and medicine [371].

The genome is not a clear and distinct set of genes separate and unique that, changing randomly but surely, determines the unchangeable characteristics of an individual. Therefore, it is unthinkable to a genetic engineering in the narrow sense, namely the idea of addressing the health and disease as an engineer approaches any machine that knows the millimetric parts that compose it. Thinking of replacing a piece, a gene in the genetic network, implies to know exactly all the multiplicity of interactions that single gene sets with the rest of the network. Knowledge that no one has, and that is not expected we will have available in reasonable time, especially if much of the research is so determined to use the reductionist paradigm. This is not to say that classical genetic and genetic engineering are not the same useful and necessary. They are useful to increase the knowledge and the possibility of intervention, but without spreading the fable of treating diseases such as replacement of ill and failing parts (genes) and without thinking of genes as a puppeteer, projects or simple vehicle of fix informations. Genes are active all the moments of our lives; they turn on and off each other and react to the environment. The molecular level demands a systemic approach. Looking back, we can say that thanks to the knowledge accumulated by the reductionist method, mechanistic and reductionist paradigm is entered in crisis. This is not a contradiction, is the reality that works dialectically.

### Epistemological effects of industry

We are experiencing a very delicate and new situation in our story that had never made over the centuries: the decisive presence of the industry in the scientific field, and in medical science in particular. The huge influx of industry, that is the technique oriented by profit, is a destabilizing factor of the dominant medical model [98]. The profit-oriented technical method, managed and replicated by major private systems, undermines the medical paradigm, not only because health has become a big business, and therefore a good that produces value for those who run it, but especially because it distorts the normal mechanisms of knowledge [372-376]. The mechanisms that scientists use to discover the “truth”, which, in medicine, means adequate and plausible representation of pathophysiological processes, the genesis of diseases and their possible prevention and treatment. Today the industry is a powerful medical and philosophical school, which guides the ideals and scientific research, setting standards of testing, pre-determining many answers.

It's the case even of the world of echocardiography that we use to asses endothelial function through CFR. We are witnessing a dramatic and expensive technological advancement, which aims to make perfectly measurable every aspect of cardiac function. This is obviously important, but in many cases it is not necessary in order to take clinical decisions. The resources may be optimized differently. In fact, the brain and medical knowledge are able to synthesize many more data of a machine, and to estimate with great accuracy using the simple “naked eye”, much information, as shown by several studies about ejection fraction parameter [377-382].

While the world of Epigenetics and PNEI are changing radically the way of thinking about human life, on the other hand, the structure of medical knowledge, which determines the research, the health professions training and the medical structure, resists to change [383]. The effects are very painful and obvious, and recently have been summarized by Marvasati *et al.* [384]. Poor results, unsustainable costs,

frequent medical errors, low satisfaction of patients and doctors and worsening inequalities in health. And again, the current medical model ignores the complex origin of diseases, medicalizes risk factors, makes “sick” asymptomatic persons, facilitating drugs treatments, decreeing the failure of prevention and, at the same time, the supremacy of patentable therapies that allow a profit. There is a tendency to a diagnostic inflation, leading to unjustified and inappropriate pharmacological treatments [385,386]. And this happens even in cardiology and oncology. For example, the American guidelines on the treatment of dyslipidemia lead to administer statins unnecessarily to one out of three adults [387-389], regardless of any study and any behavioral methodology relating to prevention of psychological stress that, as we have seen, increases the value of cholesterol. In the field of oncology is stated that many screening methods are able to identify “clinically insignificant tumors” with an increase of inappropriate treatments [390-392], the results of which are still scarce [393]. Research is providing more and more effective diagnostic tools. They are like increasingly powerful glasses - but needing glasses in the first place means not being able to see very well. The improvement of our investigative and diagnostic capability allows us to recognize early stage or mostly stable diseases in asymptomatic individuals. These patients are treated according to results from research conducted on more severe and acute conditions (overtreatment induced by over diagnosis). For example, the increased number of diagnoses of pulmonary embolism did not reduce the incidence of death, but increased the number of bleeding from subsequent anticoagulation therapy [394]. To avoid potential legal issues, we are doing more, with the risk of doing worse [394]. The model of medicine applied in acute situations does not match the needs of chronic diseases treatment. The striking example of this aspect comes from the lack of benefits of coronary revascularization compared to optimal medical therapy, in the case of stable coronary artery disease, although angiographically critical [395-398], or from the evidence that prolonged dual antiplatelet therapy following drug eluting stent increases major bleeding but is not associated with a decrease in composite rates of death or myocardial infarction [399,400].

“You can make a lot of money, telling healthy people who are sick,” said Moynihan, describing these phenomena [401,402]. The same mechanism has been well described by three distinguished doctors of international reputé as Marcia Angell [403-405], Jerome Kassirer [406,407] and Richard Smith [408]. The most important thing of all processes described by these Authors, is that the industry is a conditioning factor of knowledge. It's clear that if the research world is in the hands of the industry, the epistemological field, namely the definition of the questions to meet by researchers and scientists, and also how they respond, it will be structured and shaped by the pharmaceutical market needs. This means that we can do without industry and drugs? Obviously not. According to the Authors mentioned above, we can imagine a simple public control of the companies, which produce no candy, but goods essential to health. In addition, there's the need to stop the pollution of scientific knowledge by industry to allow medical science to be free to move forward [409].

**Ignoring the network perspective, continuing with a reductionist approach causes problems even in the world of medical emergency. The concrete example of the adrenergic receptors and inotropes**

Inotropes have been fundamental to resuscitation of acute cardiogenic shock or for refractory heart failure treatment for decades



[410,411]. While inotropes successfully increase cardiac output, their use is associated with an increased mortality [412], the risk of severe arrhythmias [413], increasing myocardial oxygen consumption [414] and possible myocardial ischemia [415,416]. Although different papers, based only on strictly hemodynamic pathophysiological assumptions, try to suggest the correct indication of use for each available inotropic drug, none of these considered the systemic effects of circulating catecholamines [417], how the adrenergic receptors are distributed in the heart [418-421] and in the PNEI network [422-429], that their stimulation promote apoptosis and inflammation [430-435] or how they are up- or down-regulated [436] according to other drugs [437,438], neurohormonal influences [439-444] or in case of a disease state [445-449]. A same drug could produce, from this point of view, different and opposite effects according to adrenergic receptors distribution or expression [450]. There's also evidence that the epinephrine seems to cause more harm than good even in case of cardiac arrest [451,452]. Furthermore, a patient with an extensive acute myocardial infarction loses a part of his heart and the respective receptors, potentially making a drug less effective than another that would act in other vital areas [453]. Finally, the inotropic response to dobutamine may be reduced in patients previously treated with a beta-blocker. In a randomized, short-term study, pretreatment with carvedilol markedly reduced the inotropic response to dobutamine, whereas metoprolol had only a slight inhibitory effect. This difference may be due to the observation in experimental models that metoprolol, but not carvedilol, results in beta-1 receptor upregulation [454].

There's the pressing need for new inotropic agents that avoid some of the harmful effects of those actually available. New agents will be designed to improve systolic myocardial performance and we think that they will have to be projected and tested in models similar to the specific biological and clinical condition of their future use. This could be useful to optimize and amplify the new drugs effects, limiting their side effects, dosages and costs.

### The network perspective for future researches in heart transplantation. PNEI signals: a common soil for donor and recipient

Rejection and coronary artery vasculopathy (CAV) is a complex disease with an unrevealed pathogenesis, that limits the long-term success of heart transplantation. As recently described by van de Hoogen *et al.* [455], rejection and CAV are not induced only by the donor or recipient but, nowadays, it is clear that there is some kind of synergic interaction between recipient and donor cells, which accelerates the pathogenesis of rejection or CAV [456-458].

To understand the details of this process, future research should consider a basic concept. The heart is inserted into the PNEI network and in it is inscribed the price of the accommodation to stress, the allostatic load, which is the wear and tear that results from chronic overactivity or underactivity of allostatic systems, during the individual life (extracellular matrix danger signals, cellular stress and PNEI system responses [459]). So we have to imagine that, at the time of the transplant, the recipient will have a particular psycho-neuro-endocrine-immune activation mode and functioning, which contributed to heart disease and led to heart failure. At the same time, in the heart of the donor, within cells and blood, are present PNEI molecules, circulating micro-RNAs and "allostatic signals": traces of how the physical and psychological stress (including death itself) have acted in the course of his life. These sensors and mediators will interact with the PNEI

network of the recipient and will be received by the same, starting a new dialogue and establishing a new balance.

On this basis, it is scientifically possible to consider that a part of the rejection process and of the pathogenesis of CAV can be linked to a rejection of the receiver to memories or feelings of stress of the donor. And this could also enable future studies to clarify the molecular basis of the personality changes of heart transplant patients taking attitudes and memories of the donor, without ever being aware of his history or that they had no information about [460-462].

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