

Oxidative stress: a common denominator in every pathogenesis

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As medical doctors, we are expected to be the champions of health and the slayers of disease. Essential to the success of this battle is an understanding of, and insight into, the chemistry that allows you the opportunity of reading this article. It is not sufficient to name the parts. It is imperative that we understand how the parts work, the processes that lead to malfunctions, and how these malfunctions appear as signs and symptoms to which we eventually give a label. We have concentrated on the results of biological processes gone awry. It is time to deal with the causes.

The layperson would better understand oxidative stress as a sort of **biological rusting process**. Rusted components cannot function optimally nor efficiently. Rusting accelerates the demise of the object or, on a personal note, contributes to the emptying of the vital resources for health and to the consequent inevitable decline into the abyss of lifestyle and age-related chronic diseases and untimely death.

Dorland's Medical Dictionary defines **oxidative stress** as "any of various pathological changes seen in living organisms in response to excessive levels of cytotoxic oxidants and free radicals in the environment". I would like to add that the "environment" here refers to both the territory within the body as well as to the habitat in which the body resides. Oxidative stress reflects an imbalance between the manifestation of reactive oxygen species (ROS) and a biological system's ability to detoxify the reactive intermediates or to repair the resulting damage. ROS are generated by regular processes in major intracellular organelles including mitochondria, peroxisomes, and the endoplasmic reticulum (ER). These ROS-generating organelles possess highly efficient ROS scavenging machineries to maintain what I term "oxidative homeostasis under standard biological conditions".

Moreover, ROS generation is part of the cellular response to xenobiotics, cytokines, pathogen invasion, heavy metals, water and/or mineral imbalances, extreme temperatures, pollution, dietary components, smoking, and psychological stress, amongst others. Overwhelmed and nutritionally depleted systems inevitably malfunction leading either to an increase in ROS generation and/or a decrease in the ROS scavenging operations. A major consequence of this predicament is an accumulation of misfolded/aggregated proteins in the mitochondria and the ER. In simple terms, it becomes impossible to build successfully since the building-blocks either do not fit where they should, or

do not perform as expected. The project is doomed to decay and consequent collapse.

ROS also function as critical signalling molecules in cell proliferation and survival. Researchers have coined the term "**oxidative interface**" to describe that boundary between ROS and the signalling molecules they activate. Cellular signalling pathways regulated by ROS affect a variety of cellular workflows such as proliferation, metabolism, differentiation, survival, antioxidant and anti-inflammatory response, iron homeostasis, and DNA damage response. As with so many other biological entities, ROS can be either a friend or a foe. For example, ROS regulates proliferative and apoptotic pathways, and the formation of tumours is partly caused by the abnormal synchronisation of proliferation and apoptosis. Balance is one of the obvious principles for survival demonstrated by the contents of the universe we live in. Here again, the stability of normal function finds its equilibrium on a knife's edge.

In everyday practice you will look oxidative stress in the face whenever you are confronted with the molecular damage it causes as a major contributor to the development of diabetes, atherosclerosis, Parkinson's, Alzheimer's, autoimmune diseases, cancer, depression, ageing, and more. A quick search of your arsenal will reveal a lack of weapons to fight this enemy. At this stage it proves beneficial to adjust one's mindset. We have briefly identified the problem and I have spent about half of the number of words allowed for this article. Let us turn briefly to identified solutions and place them in two distinct groups, namely **lifestyle measures** on the one hand and **nutritional supplementation** on the other.

Lifestyle measures include potential beneficial modifications aimed at reducing the formation of free radicals. These are related to diet, drinking, exercise, smoking, physical and psychological stressors, work and leisure environments, and relationships. Generally, these steps prove difficult to implement in the long term, primarily due to human misguided ability to develop an extreme reluctance towards taking responsibility for one's own body. This, however, must not deter us from dispensing essential and life-saving advice. Ultimately, the patient must understand that he/she is the manager of his/her own health, we are just coaches, not magicians.

Basic dietary guidelines include the avoidance of high glycaemic foods (foods that are high in refined carbohydrates and simple

sugars), and of processed meats such as sausages, bacon, and salami. Reusing cooking fats and oils should not be practised. Alcohol should be limited, but since the meaning of "limited" is dependent on the individual patient, it is preferable to avoid alcohol altogether. Eat foods rich in antioxidants and/or substances which possess antioxidant properties. Generally, these include fruit, broccoli, carrots, tomatoes, nuts, onions, parsley, legumes, peppers, beets, spinach, etc. I will not spend much time on these guidelines as they are universally known, albeit largely ignored. The cessation of smoking is not negotiable. Moderate exercise programmes personalised to individual abilities are essential. The avoidance of environmental free radical exposure such as pollutants and chemicals is advisable, even if not always possible.

The scope of the present article does not permit an extensive overview on the neglected area involving the **conversion of psychological stress into the cellular stress response**, and on the link between ER stress and mental disorders, but I wish to dedicate at least a paragraph to this vital understanding. This will address what patients generally call "stress" and "depression", involving relationships, career, finances, and their uniquely individual perspectives of life's challenges. In a nutshell, psychological stress contributes to the increase in stress-response hormones such as cortisol and adrenaline, and in cytokines (a category of signalling molecules that mediate and regulate immunity, inflammation, and haematopoiesis) such as IL-1, IL-6, and TNF- α . This increase occurs partly via the activation of the HPA axis, causing inflammatory reactions (i.e. oxidative stress) in various peripheral organs. Cytokines released in the brain or transported from peripheral organs activate microglia in the brain, which in turn release several pro-inflammatory cytokines, such as IL-1 α , IL-1 β , and TNF- α , leading to the accumulation of ROS in the brain, the consequent molecular damage, and interference with normal functioning. Moreover, social interactions that result in psycho- and physiological stress promote the expression of molecular chaperones leading to dysfunction in gene transcription and consequent increased vulnerability to mental disorders. Every doctor should address each patient's **"emotional health"** despite their original presenting complaint, and recommend that, regardless of how difficult it may seem to the patient, it is vital that he/she addresses the cause or causes of the challenges. Pharmaceutical treatment does not address the causes of the problem, and the development into responsible, society-contributing adults involves the growth that can only be obtained from having exercised one's "psychological muscles" against the resistance of human apathy and selfishness. The fact that a solution is difficult or not to our liking does not invalidate the solution.

Lastly, just as we can correct an iron deficiency by providing supplemental iron, it is possible to provide **supplemental antioxidants** to assist the body in dealing with oxidative stress. Here again, it is beyond the scope of this writing to delve into the chemical elegance of natural antioxidants, the intestinal absorption challenges, other routes of administration such as sublingual and intravenous, and the scientific evidence for the effects of such supplementation. Well known substances such as vitamins A, C, and E, beta-carotene, selenium, and manganese, possess antioxidant activity amongst their myriad of functions. Regarded as the body's most powerful endogenous antioxidant, glutathione can be supplemented. Cutting-edge technology has enabled certain glutathione supplements to overcome delivery and absorption challenges by making use of liposomes with proven bioavailability and beneficial effects.

In summary, oxidative stress is most likely happening in your body as you read this article. Oxidative stress is destroying the dopaminergic neurons of your patient with Parkinson's. But both your and his/her bodies were designed for health, not for disease. Consider this: We eagerly prescribe paracetamol for the common headache. However, the cause of the headache is not a paracetamol deficiency. Let us have the courage and fortitude to seek the causes of dysfunction and address them. Above all, do no harm.

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