Oxidative Stress

“We know that we must constantly consume oxygen in order to carry out normal cellular metabolism. On a cellular basis, oxygen is mostly used in organelles called mitochondria. These organelles have been called our cells' "power-plants" because this is where raw fuels that we eat (proteins, carbohydrates, and fats) are converted into a useful form of energy (adenosine tri- phosphate, or ATP) that the cell uses to carry out necessary chemical processes. This conversion process requires oxygen, which is used by the mitochondrion as an "electron acceptor".

Consequently, this vital energy production would grind to a halt if we did not constantly breathe oxygen. Even though oxygen consumption is vital for our very survival there are unfortunate consequences for using oxygen. Oxygen can be converted into very deleterious forms called reactive oxygen species (ROS), which include free radicals, the same compounds that can be formed during a nuclear explosion. It now appears that ROS constantly arise as by-products of normal metabolism. Thus, using oxygen as a central part of our metabolism is really a double-edged sword-we need it to provide energy to carry out normal metabolic processes, but we are also constantly converting some of the oxygen that we breathe into ROS that damage important biomolecules and eventually lead to cell and organ dysfunction.”(2)

“Reactive oxygen species are unstable molecules containing oxygen as a by-product of the natural metabolism of oxygen. They are very reactive and can take many different forms including NO (nitric oxide), peroxynitrite ($ONOO^-$), H_2O_2 (hydrogen peroxide), hydroxyl radical (OH^-) and hydrochlorous acid (HOCl).

The build-up of reactive oxygen species to a high level inside cells is known as oxidative stress. This causes damage to proteins, DNA and RNA and can even result in cell death. ROS biomolecules have been implicated in a variety of pathologies including include neurodegenerative diseases, cancer, the ageing process and atherosclerosis. In response to oxidative stress, the body increases production of antioxidants, such as glutathione and catalase, and these convert the dangerous free radicals into harmless molecules like water.

However, reactive oxygen species in low levels have been identified as having useful and beneficial effects. For example, they have an important role in gene expression and the regulation of cellular signaling. There is also evidence to suggest that ROS may have a role in the modulation of cell differentiation, including the hemopoietic differentiation involving stem cell production, in both pathological and physiological conditions.

Reactive oxygen species are produced from many intracellular processes including from cell mitochondria and NADPH oxidases (NOX enzymes) linked to neutrophils. Neutrophils are white blood cells which produce high levels of ROS as part of their defense role. ROS is also produced by a broad variety of enzymes, including nitric oxide synthase, xanthine oxidase, lipoxygenases, cyclooxygenases and cytochrome P450 enzymes.

Exogenous stimuli further induce oxidative stress, for example alcohol leads to formation of reactive oxygen species during its degradation and activates cytochrome P450 enzymes which induce ROS production. Tobacco smoke also induces ROS because it contains free radicals that react with oxygen to form ROS. Ultraviolet light is also an exogenous inducer but is less avoidable than alcohol or tobacco smoke. Inducing reactive oxygen species

increases the oxidative damage to cellular components and therefore contributes to the development of skin cancer."[1]

It is become increasingly clear that reactive oxygen species (ROS), including free radicals are involved in cardiovascular disease and in the aging process itself. The ROS are common by-products of many oxidative biochemical and physiological processes. They mediate various signaling pathways that underlie vascular inflammation in atherogenesis.

Many other diseases have been implicated such as Alzheimer's, asthma, COPD, and Parkinson's disease to name but a few. Whereas ROS are essential for normal cellular processes, the molecular effects of increased ROS include the oxidation of DNA, RNA, lipids and proteins resulting in the dysregulation of ion channels, signaling pathways and transcription factors.

Mutations of the MTHFR gene (methylation defect) increase oxidative stress as can all types of trauma or stress. Elevated homocysteine probably induces production of oxygen free radicals, so a moderate increase in homocysteine is associated with cardiovascular disease but homocysteine cannot be considered completely responsible for oxidative damage. It cannot be proven yet if homocysteine causes or is the result of vascular damage. It seems likely that the increased oxidative stress from defects in the pathway lead to increased vascular damage and consequent elevated homocysteine.

Significant increase in free radicals are noted in both diabetes 1 and 2, with the onset associated with oxidative stress, but the mechanism is not certain. Oxidative stress by-products contribute to insulin resistance. Insulin resistance, impaired glucose tolerance, and overt diabetes are associated with an increased risk of cardiovascular disease. Because all these conditions are also accompanied by the presence of an oxidative stress, researchers propose oxidative stress as the pathogenic mechanism linking insulin resistance with dysfunction of both beta cells (in the pancreas) and endothelium (lining of blood vessels), eventually leading to overt diabetes and cardiovascular disease. This hypothesis, moreover, may also contribute to explaining why treating cardiovascular risk with drugs, such as ACE inhibitors and statins, all compounds showing intracellular preventive antioxidant activity, results in the onset of new cases of diabetes being reduced.

Autonomic imbalance, which is characterized by a hyperactive sympathetic system and a hypoactive parasympathetic system, is known to be associated with various pathological conditions. Over time, excessive energy demands on the system can lead to premature aging and diseases. Autonomic imbalance may be a final common pathway to increased morbidity and mortality from a host of conditions and diseases, including cardiovascular disease. Heart rate variability may be used to assess autonomic imbalances, diseases and mortality. There is evidence linking heart rate variability to established and emerging modifiable and non-modifiable cardiovascular risk factors such as hypertension, obesity, family history and work stress. The theory of autonomic imbalance may provide a unifying framework within which to investigate the impact of risk factors, including psychosocial factors and work stress, on cardiovascular disease, and this is discussed separately in "Inflammation and Autonomic Dysfunction."

Modern techniques of cardiovascular risk assessment such as retinal photography and carotid intimal thickness scanning, as well as more established techniques such as coronary CT angiography can be utilized to watch changes occurring in our vasculature. Retinal photography provides a look at the small blood vessels in the brain, with the intimal scanning

the larger vessels. If there is a significant cardiovascular risk, CT scanning or formal coronary angiography may be needed.

Studies have now demonstrated an interaction between endothelial (inside lining of arteries) function and oxidative stress. The vascular endothelium is involved in the release of various vasodilators, including nitric oxide, prostacyclin and endothelium-derived hyperpolarizing factor, as well as vasoconstrictors. Nitric oxide plays an important role in the regulation of vascular tone, inhibition of platelet aggregation, and suppression of smooth muscle cell proliferation. Endothelial dysfunction is the initial step in the cause of cardiovascular disease, and it is well known that the grade of endothelial function is a predictor of cardiovascular outcomes. Several mechanisms contribute to impairment of endothelial function. An imbalance of reduced production of Nitric oxide or increased production of reactive oxygen species, mainly superoxide, may promote endothelial dysfunction. One mechanism by which endothelium-dependent vasodilation is impaired is an increase in oxidative stress that inactivates Nitric oxide.

The majority of cardiovascular diseases cause progressive deterioration, mainly resulting from accumulation of vascular and myocardial tissue damage. A growing body of evidence indicates that oxidative stress and the inflammatory response are involved as triggers or mediators of these tissue injuries. It is well known that atherosclerosis is an inflammatory disease where the arteries become thicker and plaque builds in areas of damage. Bacterial infections such as Chlamydia pneumoniae and cytomegalovirus can also cause the inflammatory response in the coronary arteries, and accumulation of macrophages in the vascular wall promotes plaque formation. Current cardiovascular research in “Minoca” is looking at microemboli and accompanying inflammatory damage.

In myocardial infarction, infiltration of macrophages and neutrophils may modify myocardial injury even after reperfusion. It is also reported that inflammatory cytokines and growth factors are activated in either ischaemic or non-ischaemic chronic heart failure. In such progressively deteriorating conditions, both oxidative stress and the inflammatory response are synergistically involved, causing a vicious cycle of progression of injury. These considerations support the hypothesis that inflammatory response is involved in most progressive cardiovascular diseases.

Management I believe revolves around removing risk factors, most of which are environmental or lifestyle related. Some, like the inherited traits of methylation defect appear to be managed with suitable vitamin supplementation, while in others increased surveillance and early treatment is required. There is certainly a place for medication, in particular the statins (here the much- maligned Crestor and Lipitor) and ARB inhibitors in diabetes and cardiovascular disease. Nathan Pritikin was able to prove he could achieve similar vascular improvements, but the lifestyle change alone needed for this is extreme. Less extreme is a move towards the lifestyle found in some of the Mediterranean islands and thus the so-called Mediterranean diet has evolved. The changes adopted here have been demonstrated conclusively to be very helpful. Sadly our community wants the easy way out with a pill for every purpose. Many purveyors of micronutrients and vitamins use scare techniques to promote products that have shown to have little or no demonstrable benefit.

The closer we move towards eating food gown by ourselves or as close as possible to market purchased, avoiding food that has been stored in supermarket cold rooms, the better.

It seems obvious, but smoking must be avoided, as should processed foods, pollutants, toxins and preservatives. Care must be taken with animal protein where hormones, growth enhancers and other chemicals are utilized.

Food needs to be high in anti-oxidants, beta-carotene and vitamins A,C and E, but not necessarily supplements as these much less effective. In particular foods such as broccoli, tomatoes, carrots, berries should be eaten. Green tea and red wine are helpful. If you have food intolerance, the causative foods need to be removed from the diet, as eating food your body sees as a threat induces inflammatory responses with potential for long term disease progression.

Activity such as tai-chi and meditation are recommended. Care should be taken with muscle-damaging anaerobic exercise, and while increased aerobic exercise is beneficial, endurance exercise is not.

Reference:

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