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Can free radicals be good for you?

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Free radicals – the bad guys

It is widely held[1] that free radicals are involved in the initiation and propagation of many and various illnesses, including cancer, heart disease, stroke, rheumatoid arthritis, diabetes, and multiple sclerosis (MS). The list runs on, and even the process of ageing itself is believed to be driven by free radicals, also called reactive oxygen species (ROS) or reactive oxygen intermediates (ROI). Now, the species classified as ROS or ROI are derived from molecular oxygen (O_2) which obviously we need to breathe to stay alive. In the main, ROS are the superoxide radical anion ($O_2^{-\cdot}$), its conjugate acid, the hydroperoxyl radical ($HOO^{\cdot}$), the hydroxyl radical ($HO^{\cdot}$), organic peroxyl radicals ($ROO^{\cdot}$), alkoxyl radicals ($RO^{\cdot}$) as *bona fide* free radical (unpaired electron) molecules, but also included on the list are molecular (especially, singlet) oxygen (O_2), organic hydroperoxides, ROOH and hydrogen peroxide itself, H_2O_2. It can be said that all oxygen free radicals are ROS/ROI but not all ROS/ROI are free radicals. As respired O_2 enters living cells it is metabolised *e.g.* by the mitochondria to $O_2^{-\cdot}$, which is not in itself strongly oxidising, but it provides a source of other ROS. To avoid living cells being overwhelmed by $O_2^{-\cdot}$, they contain the enzyme superoxide dismutase which catalyses the reaction [equation (1)]:

$$2O_2^{-\cdot} + 2H^+ \rightarrow H_2O_2 + O_2 \qquad (1)$$

Now H_2O_2 is not harmless in cells since it can provide a source of $HO^{\cdot}$ radicals, particularly if there is free iron present, which promotes the Fenton Reaction [equation (2)]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\cdot} + {}^{-}OH \qquad (2)$$

$HO^{\cdot}$ radicals can attack sensitive molecules in cells, including membrane lipids, carbohydrates and proteins and, if they are formed in the cell nucleus,

DNA bases too, potentially leading to strand-breaks and cell mutations. The attack of $HO^{\cdot}$ and other kinds of radicals on lipids can initiate the process known as lipid peroxidation, which is responsible for the rancidification of foodstuffs including meat. That our human "meat" does not become rancid while we remain alive is due to the fact that living cells contain antioxidants, in particular, catalase which is a common enzyme found in nearly all living organisms that are exposed to oxygen. Catalase is able to catalyse the decomposition of hydrogen peroxide to water and oxygen, and has one of the highest turnover numbers of all enzymes – one catalase molecule can convert 40 million molecules of hydrogen peroxide to water and oxygen per second. Glutathione peroxidise also catalyses the decomposition of H_2O_2 by combining its reduction to water with the oxidation of reduced glutathione (GSH), a thiol-containing tripeptide (glu – cys – gly) [equation (3)]:

$$H_2O_2 + 2GSH \rightarrow GSSG + 2H_2O \qquad (3)$$

The product, oxidised glutathione (GSSG), contains a disulfide bridge, and can be converted back to GSH by glutathione reductase enzymes. It is now thought that peroxiredoxins may be even more important[2] in removing H_2O_2 from cells in animals, bacteria, and probably plants. There are at least three classes of these enzymes, but in the function of all of them a cys-SH group present on the peroxiredoxin is oxidised by H_2O_2 to a sulfenic acid, cys-SOH. The interception of ROS is not perfect and around 1% of respired O_2 ends-up as ROS. Over a year this amounts to 1.7 kg of ROS, since humans are fairly large animals and breathe substantial amounts of oxygen. To cope with what ROS remain, there are both intrinsic and extrinsic antioxidants present in cells, the latter being brought into the living organism and hence its cells by ingestion, *i.e.* in our food and in the form of deliberately taken dietary supplements. The effectiveness of latter is debatable, however, as shall shortly become evident. Many molecules that are designated as antioxidants possess phenolic groups, *e.g.* the vitamin-E series and compounds present in green tea, principally epigallocatechin gallate (EGCG). It is thought that such materials can act as chain-breaking antioxidants, in which the chain of free radical propagation is "broken" by transfer of an H-atom from a phenolic OH moiety to an $ROO^{\cdot}$ radical [equation (4)]:

$$ArOH + ROO^{\cdot} \rightarrow ArO^{\cdot} + ROOH \qquad (4)$$

This effectively deactivates the $ROO^{\cdot}$ radical from abstracting an H-atom from a lipid unit to give a carbon-centred radical, which by the addition of O_2 would form another $ROO^{\cdot}$ radical to propagate the autoxidation process [equation (5)]:

$$ROO^{\cdot} + RH \rightarrow ROOH + R^{\cdot} \qquad (5)$$

The door to the field of free-radical toxicology was set open in the proposal by Gerschman *et al.* in 1954[3] that oxygen poisoning and the effect of X-irradiation on animals had a common mechanism which involved the

formation of free radicals. Two years later, Denham Harman suggested that the ageing process too was mediated by free radicals[4]. The abstracts of these two classic papers are as follows:

Abstract: A consideration of various isolated reports in the literature has led us to the hypothesis that oxygen poisoning and radiation injury have at least one common basis of action, *possibly through the formation of oxidising free radicals*. This article reviews the pertinent material that led to this hypothesis and also presents the supporting evidence obtained from (i) experiments on the protective action against oxygen poisoning by substances of varied chemical nature known to increase resistance to irradiation, and (ii) experiments on the survival in oxygen of mice irradiated and exposed to high oxygen tensions simultaneously or at different intervals.[3]

Abstract: This paper describes a theory about mechanisms of aging that is based on free radical chemistry: "Aging and the degenerative diseases associated with it are attributed basically to the *deleterious side attacks of free radicals on cell constituents* and on the connective tissues. The free radicals probably arise largely through reactions involving molecular oxygen catalyzed in the cell by oxidative enzymes and in the connective tissues by traces of metals such as iron, cobalt, and manganese."[4]

These ideas and their broader ramifications underwent a gestation period, with periodic mention, leading to a seminal paper by Trevor Slater and his colleagues in which an explanation for the toxicity of carbon tetrachloride (CCl_4), principally to the liver, was advanced in terms of a free-radical mechanism[5]. For those chronically exposed to "carbon tet" over lengthy periods, damage to the liver was not infrequent and in some cases, liver failure occurred, in addition to neurotoxic effects of CCl_4, and potential links to liver and kidney cancer. CCl_4 used to be widely employed in the dry cleaning industry and was also commonly used as an organic solvent, but due to its toxicity has been largely superseded by safer materials. The mechanism of activation involves a reductive elimination of Cl^- from CCl_4, (*e.g.* by cytochrome P450 enzymes) which forms a $CCl_3^{\bullet}$ radical. The $CCl_3^{\bullet}$ radicals can then add O_2 to form $CCl_3OO^{\bullet}$ radicals, which are particularly reactive versions of peroxyl radicals. This enhanced reactivity can be viewed in terms of the limiting canonical structures: $CCl_3OO^{\bullet} \leftrightarrow CCl_3O^{+\bullet}O^-$ which for common $ROO^{\bullet}$ radicals, normally contribute around 50 : 50 to the overall structure. However, the three strongly electron withdrawing Cl-atoms tend to disfavour the second structure, with the positive charge on the O-atom adjacent to the CCl_3-group, and so the unpaired electron becomes increasingly localised onto the terminal O-atom according to an increased weighting of the limiting structure $CCl_3OO^{\bullet}$ [6]. An increased localisation or "exposure" of the unpaired electron tends to engender a more reactive radical character and so the H-atom abstraction reaction [equation (5)] is

facilitated. Thus the lipid peroxidation process overall is encouraged, causing severe damage to the liver cells so that the organ becomes cirrhotic and ultimately fails.

Good free radicals?

Recent research[7] published from King's College in London indicates that mice deliberately bred to possess more of an enzyme (NADPH oxidase-4) that actually produces ROS, including free radicals, suffered less heart disease than animals in which the enzyme had been "deleted". This rather runs counter to the prevailing argument espoused above but it is thought that exposure to ROS can actually "toughen-up" an organism, so that it becomes more resistant to certain conditions like cardiovascular disease. It is well known that ROS, including superoxide, can act as cell-messengers, and so in concentrations that do not overwhelm the protective antioxidative capacity of the organism they may be beneficial. Some of the ROS may act as signalling agents to operate protective pathways, for example in enhancing myocardial angiogenesis, which is the physiological process involving the growth of new blood vessels from pre-existing vessels. The latter is a critical determinant of cardiac adaptation to overload stress. Several years ago, another group of London researchers, this time from University College (UCL), reported that the basic theory underlying the toxicity of oxygen radicals is flawed[8]. White blood cells, or leukocytes (also spelled "leucocytes", *leuco-* Ancient Greek "white"), are cells of the immune system that participate in defending the body against infectious diseases and xenobiotics (foreign agents). Five different kinds of leukocytes are known, all of them stemming from a multipotent cell termed a haematopoietic stem cell, which exists in bone marrow. Leukocytes are found throughout the body, and are present in the blood and lymphatic system, with a typical lifetime of 3–4 days. Leukocytes comprise *ca* 1% of the blood of a healthy adult, and the leukocyte count is often an indicator of disease, being raised (leukocytosis) above the normal levels of $4 \times 10^9 - 1.1 \times 10^{10}$ white blood cells/litre. The name "white blood cell" derives from the observation that after a blood sample has been centrifuged, the white cells are found in the *buffy coat*, a thin layer of nucleated cells between the sedimented red blood cells and the blood plasma, which is normally white in appearance.

Leukocytes produce oxygen ROS, and the process by which they do so is vital for killing microbes efficiently. In some people, the process is defective, rendering them liable to chronic, severe and often fatal infections. Accordingly, the inference has been drawn that the ROS are themselves highly toxic, and must be harmful to human tissues if they are sufficiently virulent to kill organisms as robust as bacteria and fungi. In contrast, the UCL group found that it was not ROS that made white blood cells so destructive but the release of enzymes (proteases) with the power to digest

foreign invading species. The enzymes are triggered by a flow of K^+ cations within the cell. When the process was blocked using iberiotoxin (derived from scorpion venom) and paxilline (a fungal mycotoxin), the cells were no longer able to combat pathogens, demonstrating that the ROS are not as toxic as previously thought[8]. The paper concludes: "These data have significance beyond the inherent value of defining the precise molecular mechanisms involved in a physiological process of paramount importance to survival. The perception that neutrophils kill microbes through toxic oxygen radicals and their metabolites provided much of the biological basis for the theories relating the toxicity of oxygen radicals to the pathogenesis of a wide variety of human diseases, and the development of antioxidant drugs for their treatment. These theories and treatment merit re-evaluation."

Noteworthy too is a study[9] by researchers at McGill's Department of Biology, who tested the accepted "free radical theory of ageing" by creating mutant worms with an increased production of ROS in their bodies. It was found that in contrast to the expected outcome, the worms lived longer than normal worms. Even more significantly, when the mutant worms were treated with antioxidants, *e.g.* Vitamin C, their lifetimes were shortened. The researchers then sought to mimic the apparent beneficial effect of the free radicals by treating regular, wild worms with Paraquat, a herbicide that generates superoxide and hence other ROS, by redox-cycling. Paraquat is so toxic to humans and animals that it is banned in the European Union and its use is restricted in many other parts of the world. Remarkably, they discovered that the worms lived longer after being exposed to Paraquat. It is thought that in the genetically modified worms, the production of ROS can help to trigger the body's general protective and repair mechanisms, thus acting to preserve life. Whether one can extrapolate these results for worms to far more complex organisms such as humans is a moot point, of course.

Antioxidant supplements

It is widely held that a "Mediterranean Diet" is very healthy since the incidences of cancer and cardiovascular diseases in the Mediterranean are lower than in the colder northern countries. This is the basis of the "five a day" diet, in which it is recommended that we consume five 80 g portions of fruit and vegetables daily. An explanation for this, which has entered the public consciousness, is that a diet rich in fresh fruit and vegetables is full of antioxidants and, by mopping-up free radicals, is protective against these particular maladies. This must be qualified by a recent European study which found a relatively small reduction in the overall cancer rate according to their intake of fruit and vegetables in a sample of almost half a million people[10]. However, in an extension of this line of thinking, a massive multi-billion dollar industry has developed which supplies pure antioxidant compounds in the form of pills and capsules to be taken as dietary

supplements. In the USA alone, more than half of all adults take some form of vitamin or mineral supplement, at a cost of £23 billion/year[11]. Now, not only is there precious little hard scientific evidence that taking these compounds additionally and above what is present in the diet actually does any good, it is quite possible that in too high a dose some of them can have adverse effects. The pioneer protagonist of such dietary supplementation was Linus Pauling who recommended taking Vitamin C (L-ascorbic acid) in large amounts. He did live to be 93. L-ascorbic acid (or L-ascorbate) is an essential nutrient for humans and certain other animal species[12]. In living organisms, ascorbate is thought to act as an antioxidant by protecting the body against oxidative stress. Ascorbate is a cofactor in at least eight enzyme-catalysed reactions, including a number involved in collagen synthesis, and when they do not function properly the disease known as scurvy arises. In animals, these reactions are especially important in wound-healing and in preventing bleeding from capillaries. The nickname given by Americans to the English, "Limeys", derives from the practice of taking lime-fruits on board ships in the British Navy so that sailors could drink the juice (which is now known to contain Vitamin C) and offset the symptoms of scurvy which had formerly beset them on long sea voyages. While the daily recommended dose of 40–95 mg/day is sufficient for the needs of a human adult, doses of 10–100 times this amount have been advocated by some practitioners. There is, however, no clinical evidence that such megadoses protect against developing cancer, coronary disease or the common cold, and indeed might be harmful, *e.g.* in promoting kidney failure[12]. Most of the excess Vitamin C is simply excreted from the body (occasioning diarrhoea) so it is unlikely to do much good.

The most infamous case of a dietary supplement proving actually harmful is the Beta-Carotene and Retinol Efficacy Trial (CARET) in which daily β-carotene (30 mg) and retinyl palmitate (25,000 IU) were given to 18,314 participants who were at high risk for lung cancer because of a history of smoking or asbestos exposure[13]. The study was stopped ahead of schedule in January 1996 because participants who were randomly assigned to receive the active intervention were found to have a 28% increase in incidence of lung cancer, along with a 17% higher death-rate and a higher rate of death from cardiovascular disease compared with participants in the placebo group. The notion that beta-carotene could be protective against cancer stemmed from the observation made in the 1970s that people who ate a lot of carrots had a lower cancer rate than the average. I seem to remember that drinking carrot-juice was quite popular at this time, and that some people who overdid their consumption of it found their skin turned orange in places! However, there are many other substances present in actual plant material, which might act in some as yet unknown fashion in regard to inhibiting the development of cancer. In the early 1990s, trials of Vitamin E looked to be a resounding success in regard to preventing heart disease. In two studies involving over 127,000 people, it was found that those

who consumed a diet rich in Vitamin E had a significantly (40%) lower incidence of cardiovascular disease than those who didn't. It was found that the addition of Vitamin E to blood samples *in vitro* seemed to protect LDLs against oxidation, which was believed to be a central modality in the development of heart disease. Sales of Vitamin E soared, with 23 million Americans taking it by the end of the decade, and yet the results of various studies on Vitamin E supplements rather than as present naturally in the diet, are inconsistent in terms of overall health benefits[11,14].

The Alpha-Tocopherol, Beta-Carotene (ATBC) Trial[14] was a cancer prevention study conducted by the US National Cancer Institute (NCI) and the National Public Health Institute of Finland from 1985 to 1993. Its aim was to determine whether certain vitamin supplements would prevent lung cancer and other cancers in a group of 29,133 male smokers in Finland. The participants (aged 50–69) took a pill daily over a period of 5–8 years containing either: 50 milligrams (mg) alpha-tocopherol (a form of Vitamin E), 20 mg of beta-carotene (a precursor of Vitamin A), both, or a placebo. The main results were as follows, and might be described as "mixed" in their benefits:

- Men who took beta-carotene had an 18% increased incidence of lung cancer and an overall death rate of 8%. Vitamin E had no effect on the incidence of lung cancer or overall mortality. Similar results were found for taking both supplements to those taking beta-carotene alone.
- The effects of beta-carotene appeared more adverse in men with a relatively modest alcohol intake (more than 11 grams per day; 15 grams of alcohol is equivalent to one drink) and in those smoking at least 20 cigarettes daily.
- Those taking Vitamin E had 32% fewer cases of prostate cancer and the death-rate from prostate cancer was reduced by 41%. However, death from haemorrhagic stroke was increased by 50% in men taking alpha-tocopherol supplements, primarily among those with high blood pressure.
- The results of both the trial and post-trial follow-up of the ATBC Study, in conjunction with results from the CARET Study completed in 1996, continue to support the recommendation that beta-carotene supplementation should be avoided by smokers. The possible preventive effects of alpha-tocopherol on prostate cancer require confirmation in other ongoing trials[14].

Can vitamin supplements cut the benefits of exercise?

To explore the possibility that antioxidants might interfere with the beneficial effects of ROS in preventing cellular damage after exercise, Michael Ristow[9] at the University of Jena in Germany and his colleagues recruited 40

volunteers, and asked half of them to take 1,000 milligrams of Vitamin C and 400 international units of Vitamin E per day. These quantities are equivalent to the amounts present in some vitamin supplements. The volunteers were also asked to exercise for 85 minutes a day, five days a week, for four weeks. The results from muscle biopsies showed a two-fold increase in a marker of ROS called TBARS (thiobarbituric acid-reactive substances) in those volunteers who didn't take antioxidants, but no increase in those who did take the supplements, in line with the accepted picture that ROS are generated during exercise and that antioxidants intercept them.

It is well known that exercise can promote a reduction in insulin resistance, which is a precursor condition to type 2 diabetes. However, when Ristow's team measured the effects of exercise on insulin sensitivity, they found no enhancement in those volunteers who were taking antioxidants, but a significant increase in those not taking them. Thus it might be concluded that antioxidants are preventing the health effects of exercise, though it should be noted that not all vitamin supplements contain such high doses of vitamins C and E, which are also far higher than would be obtained from eating the recommended amount of fruit and vegetables. The positive effect on health from eating fruit and vegetables may be because they contain other protective compounds, and taking vitamin supplements is no substitute for them. Malcolm Jackson at the University of Liverpool is reported as commenting[9]: "These data are fully in accord with recent work on the actions of ROS in cells, although clearly at odds with the popular concept that dietary antioxidants are inevitably beneficial."

Antioxidant therapies?

The issue of antioxidants acting as defenders of the body against ROS has been extended to their use in medical therapies[15]. If antioxidants present in the diet can protect against damage to the organism by ROS and the development of various diseases, it might be plausible to treat various illnesses with antioxidants. This at least goes the line of reasoning, which is similar to the case for taking dietary antioxidant supplements, although as we have seen this is a fairly weak case at best. However, few antioxidants including edaravone (to treat ischaemic stroke in Japan) have found accepted clinical use. Moreover, many well-known substances, including antioxidant vitamins (A, C and E), and more recently developed materials like nitrones (also used as spin-traps for radicals in electron spin resonance investigations[16]), have not unanimously passed the scrutiny of clinical trials that they are effective in the prevention and treatment of various diseases. To date, there have been several large ($>$7,000 participants) clinical trials aimed to test the effectiveness of antioxidants as cancer prevention agents specifically, none of which have been convincing[17]. A recent review[18] emphasises the complexity of cancer and its development and the importance

of eliminating as far as possible exposure to environmental carcinogens including carcinogenic metals, concluding that "prevention, as in all threatening aspects of life, being better than cure."

Positive roles for ROS?

As noted, antioxidant defences are not 100% effective, since oxidative damage to DNA, proteins, and lipids can be proven to occur in all aerobes under ambient levels of O_2. A simple explanation for why nature has not developed a means to soak-up all ROS is that they perform important roles. It is likely that evolution had to evolve a compromise of antioxidant defences that allow such roles to be played while minimising oxidative damage. ROS production in animals by phagocytes and by other cells in the gastrointestinal and respiratory tracts act to defend against microorganisms. It is well-established[2] that cellular processes are regulated by phosphorylation and dephosphorylation of enzymes and transcription factors, and as has become clear more lately, such regulation by oxidation and reduction (redox regulation) is just as important. Moreover, the two systems cross talk, *i.e.* the redox state of the cell influences phosphorylation, and *vice versa*. Binding of ligands to growth factor receptors on animal cells activates protein kinases that then phosphorylate and activate subsequent proteins in the signal cascade. Frequently and simultaneously, cellular ROS levels increase and aid the signalling mechanism. ROS tend not to stimulate phosphorylation directly but rather they increase net phosphorylation by inhibiting protein dephosphorylation. Protein phosphatase enzymes function in cells, but can be inactivated by attack from ROS. The ligand binding increases kinase activity, and the ROS assist by transiently inactivating phosphatases. As a source of ROS, the ligand may increase $O_2^{\cdot -}$ production, *e.g.* by activating suproxide-producing NADPH oxidase enzymes. These were originally described in phagocytes, but are now known to be widespread in animal and plant cells. When cells are exposed to additional amounts of H_2O_2 such as at a site of injury or inflammation or when NADPH oxidase enzymes are activated, the peroxiredoxins are partially inactivated to allow signalling. The cell smartly makes more peroxiredoxin, and reactivates the inactive form, so that the extra H_2O_2 can be removed once it has served its purpose[2]. Rather than being a consequence of a leakage of electrons, mitochondrial H_2O_2 production may provide a signal to the cytoplasm and nucleus of mitochondrial activity, leading to changes in nuclear gene transcription via redox regulation and phosphorylation of transcription factors.

Conclusions

Humans have evolved in an atmosphere containing 21% O_2, and derived therefrom, ROS are ubiquitous in ourselves and other animals, and in plants

and aerobic bacteria. Over the long human lifespan, continual and accumulated damage by ROS may contribute to the age-related development of cancer, neurodegenerative diseases, and many other disorders which ultimately urge our decline and demise. As we age, the repair of this damage seems to become less efficient. It is interesting that the concentration of oxidised protein taken from different human tissues and from rats and flies, creatures of far shorter longevity than humans, is almost constant up to about half the life-span of the species, whereupon it accumulates rapidly, and dramatically so during the last third of the lifespan[19]. In terms of a human lifespan it would seem that after around the age of 40 we oxidise profoundly and inexorably. Whether this is a cause or a consequence of ageing is arguable, since we have seen that elevated levels of ROS appeared to extend the lives of worms while treatment with antioxidants shortened them. It is likely that ROS act as agents to kill microbes and protect us against infection, although we have noted one study that showed it was the release of proteolytic enzymes rather than ROS from white blood cells that enabled them to combat pathogens[8]. ROS also play an essential and exquisite role in cell signalling mechanisms. Thus ROS may help to preserve us until our own reproductive years are concluded and the next generation has reached maturity, *i.e.* after the age when severe oxidation sets-in at around 40. Evolution is thoroughly pragmatic and unsentimental about such matters. The evidence is poor[20,21] that taking vitamin supplements unequivocally protects us against diseases and that therapies against cancer and other diseases using antioxidants are effective. Indeed, smokers should be very careful about taking some supplements, particularly beta-carotene, which appears to increase the rate of lung-cancer[13,14]. When people are actually deficient in a vitamin, giving them extra quantities up to the recommended daily amount appears beneficial, but this may have nothing to do with the antioxidant activity of the compound which may serve a variety of biological functions. Although there is convincing evidence from a study of nearly 500,000 subjects that consuming more than 200 g of fruit and vegetables per day does protect us against developing cancer, the effect is quite small (3%)[10]. This, nonetheless, translates into around 7,200 cancer cases each year just in the U.K. which if prevented represents a considerable saving to the N.H.S. especially in these stringent times. It is possible that the effect of eating a diet rich in fruit and vegetables may offer some protection against cancer by some other means than the antioxidant content of these foods[20,21]. Moreover, perhaps it is the "Mediterranean Lifestyle" overall that matters, and not only the diet. It is notable that much higher intakes of *ca* 600 g/day appeared to give a protection of as much as 11% against developing cancer[10]. However, the sample was much smaller and it seems likely that the lifestyle of anyone with such eating patterns differed in other respects too: less smoking and drinking alcohol, less meat and less saturated fat, less body fat, higher dietary fibre, more exercise, and possibly a less stressful approach to life. We note too a very recent study which indicates that while there is a

linear protective effect of consuming dietary fibre, particularly cereal fibre and whole grains against developing colorectal cancer, no significant protective effect was found from the intake of fibre from fruit, vegetables or legumes[22]. It is likely that the human body has been adapted by evolution to adjust the balance between ROS and antioxidants so finely that the intake of additional antioxidants has but a minor influence, and so the degree of oxidative damage is little reduced. In a way, it is reminiscent of the concept of "inbuilt obsolescence", that we cannot live forever and are designed not too, to make way for the newer and fresher generation on whom we place our hopes.

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