



Dr Paul Clayton's Health Newsletter

Antioxidants—Pro or Anti?

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The Paul Clayton Health Newsletter

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- All references on the back page
- Up-to-date news and design
- Pioneering and insightful approach
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Life, and ageing, used to be so simple.

Findings that older organisms, from helminths to mice to men, tend to generate more free radicals in their cells (specifically, in their mitochondria), and show more signs of oxidative damage, gave rise to the **Mitochondrial Free Radical Theory of Ageing**. This iconic theory, otherwise known as MFRTA, has been around in various versions since the mid-sixties (Harman '66); and it has been used to sell tons of antioxidant supplements.

Unfortunately, like so many other 1960s icons, MFRTA has not worn well, and in the last few years we have seen a steady stream of experimental findings that have left it, by now, fatally wounded. The titles of recent research papers such as *Mitochondrial free radical theory of aging: Who moved my premise?* (Liu et al '14), and *A midlife crisis for the mitochondrial free radical theory of aging* (Stuart et al '14), say it all. The old king is being attacked (though not by free radicals), and is about to be replaced by an upstart whose name is probably Chronic Inflammation – more of which later.

One of the lead assailants is the fascinatingly named Siegfried Hekimi at Montreal's McGill University, which happens to be my favourite North American campus. He and his fellow researchers have published a series of papers on this topic, and many of their key findings are based around the important antioxidant enzyme **superoxide dismutase (SOD)**. MFRTA predicts that animals in which this enzyme has been disabled would suffer more oxidative damage, and have shorter lives.

Hekimi, however, found that removing SODs from tiny *Caenorhabditis elegans* soil worms did not shorten their lives at all. These worms have 5 genes which code for SOD, and while turning 4 of them off had no effect on life span, turning the fifth off (sod-2) **increased** the worms' lifespan by 30% – an increase which was nullified by giving them antioxidants (Yang & Hekimi '07, van Raamsdonk & Hekimi '09). The group have more recently shown that SOD activity is

not even needed for the worms to live a normal lifespan (van Raamsdonk & Hekimi '12).

These and other pieces of evidence led them to formulate a **new hypothesis of ageing**, in which **rate of energy usage** is the key factor (van Raamsdonk et al '12). According to this theory, free radical damage in mitochondria is not so much a cause of ageing as a protective response against damage accumulated during the ageing process, which they believe is caused by excessive energy throughput. Damaged mitochondria produce less energy, and slowed energy usage slows the ageing process itself.

This would explain why SOD deletion in the worms increased their lifespan and why antioxidants nullified the effects of SOD deletion. It might also explain why so many clinical trials with antioxidants have produced null or even negative results when given to people who are already critically ill, as revealed by one recent meta-analysis (Bjelakovic et al '12).

It is only fair to point out that other meta-analyses have found conflicting findings (Manzanares et al '12), and there are many, including myself, who caution about the synthetic antioxidants used in many of the studies, and/or have advocated antioxidants for prevention rather than treatment. Nonetheless, it is clear that antioxidants are not panaceas, and may in some cases be counter-productive (Bjelakovic et al '12). So let's regroup.

Free radical generation and activity is part of being alive, and all life forms have developed multiple protective and adaptive mechanisms to cope with free radicals and other stressors. Some of these stress-responsive mechanisms (*hormetic responses*) are profoundly health-promoting. The idea is that while hugely excessive oxidative stress will most certainly kill you (you wouldn't want to live too close to Fukushima!), exposure to moderate amounts of stress switches on cellular repair / protective machinery which more than compensates for the initial damage; leading to accelerated tissue repair, better health and increased longevity.

Antioxidants—Pro or Anti? cont'd

“The problem with the anti-antioxidant argument is that it ignores history. The mid-Victorians consumed far higher levels of antioxidants than we do today and enjoyed much better health ie. slower ageing.”

Many—perhaps all—of these potentially health promoting mechanisms are mediated via an important group of proteins called, appropriately, **alarmins**. These include the heat shock proteins (HSPs), anti-microbial proteins (AMPs) and the sestrins – responses to chemical, microbial and physical stressors respectively.

I agree with Hekimi and the anti-MFRTA brigade to the extent that in people living a healthy and active lifestyle and eating a good diet, additional antioxidants would be unlikely to do any good and, if consumed in excessive amounts, could conceivably do harm.

The problem with the anti-antioxidant argument, however, is that Hekimi, like most scientific researchers, does not know his history, and what he sees in his worms is not necessarily relevant to contemporary human life. The mid-Victorian story proves him wrong—our recent ancestors consumed FAR higher levels of antioxidants than we do today and enjoyed much better health ie SLOWER ageing. Nor were the mid-Victorians the only people living this way, for at least two similar groups are known today. These are the monks of **Mount Athos in Greece** (Flynn '08), and the inhabitants of **Campodimele in Italy** (Lawson '11).

Let me restate Hekimi's argument, for it is a complex one. He holds that mitochondrial free radical formation, far from being a sign of ageing, is actually an adaptive response by the body to some other sort of age-associated damage, and that the mitochondria are 'deliberately' becoming less efficient (ie. producing less ATP and more free radicals) in order to slow down energy metabolism in the cell. He says that it is excessive energy use that causes ageing, and that slower energy use – such as occurs with calorie restriction – is the way to longer life. But in my view, the facts don't support this.



Campodimele, Italy

The inhabitants of the anachronistic communities of Mount Athos and Campodimele have much in common. They are rural, slow-paced and self-sustaining. They eat mostly what they grow themselves, and because they grow their own food, they are physically very active. They consume large amounts of fruits and vegetables, leavened with red wine and olive oil (which contains many interesting and

important compounds, not least the seco-iridoids), all of which constitute a nutrient-, antioxidant- and especially phytonutrient-dense diet. They enjoy a life expectancy which is 10 or more years longer, on average, than those of us who live modern, urbanised lives. And they are astonishingly free of the degenerative diseases that so many of us already suffer, or must anticipate.

The monks of Mount Athos spend two days every week fasting, which would support Hekimi's



Mount Athos, Greece

argument; but the inhabitants of Campodimele, and the mid-Victorians, do and did no such thing. They work hard, and consume plenty of calories – in fact, significantly more than we sluggish urbanites do.

The vast bulk of today's population lives a low-energy and micronutrient-lite lifestyle (do you want fries with that?), and is on the sub-optimal side of the nutrient curve. Most of us are multiply depleted, and need to increase the micronutrient density of what we eat to enjoy better health prospects. Whether this is through better food choices or supplementation is immaterial. Excessive antioxidant intake is bad, but we are consuming far too little of a wide range of nutrients, and especially those which we now know to be key anti-inflammatory compounds, namely omega 3 fatty acids from oily fish, polyphenols from fruits, vegetables, spices and other plant foods, and 1-3, 1-6 beta glucans derived from yeast.

I have other reasons for not buying Hekimi's argument. According to him, mitochondria deteriorate and become less efficient in order to protect us against the ageing process. But one thing that the Mount Athos, Campodimele and mid-Victorian communities have in common is a high level of physical activity; which is known to encourage the generation of new, healthy and highly efficient mitochondria in a process known as **autophagy**.

In any case, it seems to me that if the body wanted to protect itself against a high energy throughput it would simply produce fewer mitochondria, rather than making those it had less efficient. Maybe this is what is happening, for if the body slows down mitochondrial formation, then older, more damaged ones would accumulate (I'm reverting here to the old

“We should all be consuming more anti-inflammatory nutrients, and the fact that many of them are antioxidants is irrelevant.”

MFRTA theory of ageing). But if that was true, exercise (which triggers the formation of new and more efficient mitochondria and of course leads to increased energy throughput) would accelerate the ageing process, while everyone knows that the opposite is the case.

And another thing ... the herb *Gymnema pentaphyllum*, aka **Jiaogulan**. Jiaogulan was traditionally given as a tonic for the elderly and infirm, and a standardised extract (ActivAMP) has recently been shown to induce autophagy (ie. grow efficient new mitochondria), and to reverse metabolic senescence—ie. it restores insulin sensitivity, lowers plasma insulin and lipids, triggers the loss of abdominal fat and reduces the risk of cancer (Gauhar et al '12, Park et al '13). In all these respects ActivAMP reproduces the effects of exercise and is very obviously an important new (old) anti-ageing tool.

The anti-diabetic drug **metformin**, which, depending whose work you believe, either *reduces* mitochondrial efficiency so that they produce more free radicals (Annedda et al '08) or *improves* mitochondrial efficiency so that they produce fewer free radicals (Kane et al '10), is also considered to have anti-ageing effects, but is less suitable for self-experimentation as it often induces gastrointestinal problems.

More seriously, Hekimi has chosen, I think, to attack an obsolete model. The compounds he focuses on are classical antioxidants, but the emerging consensus is that it is atypical antioxidants such as the polyphenols which are key dietary pro-health elements. These are antioxidants but they have many other properties in the body, and their antioxidant impact is probably among the least of them.

More critically, they are powerful anti-inflammatory agents; and that is very important indeed, because there is a growing consensus that it is excessive chronic inflammation (not oxidation) that drives disease. There is plenty of room for confusion here, as the processes of inflammation and oxidation partially overlap. What is clear, however, is that our over-processed depleted diet and low energy lifestyles have left us very prone to chronic inflammation, thus driving the pandemics of degenerative disease now ravaging health care systems world-wide.

We should all be consuming more anti-inflammatory nutrients, and the fact that many of them are antioxidants is irrelevant.

Fries with that? ... or polyphenols

Several previous studies have found that eating meat cooked at high temperatures is a risk factor for prostate and other cancers.

A new piece of research carried out at the Fred Hutchinson Cancer Research Center in Seattle finds that consuming deep-fried foods such as French fries, fried chicken and doughnuts more than once a week appears to raise the risk of prostate cancer by around a third – and the effect seems to be slightly stronger with regard to more aggressive forms of the disease (Stott-Miller et al '14). Likely mechanisms involve the formation, at high cooking temperatures, of known carcinogens including polycyclic aromatic hydrocarbons, heterocyclic amines, acrylamide and other noxious compounds; which implies that these same foods will raise breast cancer risk in women.

This was not a prospective study; rather, it involved re-visiting data generated from two previous studies and re-analysing the dietary records of men who contracted prostate cancer versus matched, healthy controls. Such a study cannot differentiate between a causative and a merely associative link, but the fact that high temperature cooking is known to produce carcinogens is persuasive.

On the other hand – and there always is another hand in science – it is also perfectly possible and indeed likely that the men who consumed more deep-fried foods were eating fewer fruits and vegetables. This meant that they were consuming lower levels of polyphenols, which have an array of anti-cancer effects, and were thus less protected than the control group who ate fewer deep fried foods, and more fruits and vegetables.

This possibility is supported by another study of 200 men with prostate cancer. In this clinical trial, a high-potency cocktail of polyphenols given for 6 months was effective in reducing PSA levels by nearly two thirds, and slowing the progression of cancer (Thomas et al '14). This is in line with other groups' findings (ie Frattaroli et al '08, Kenfield et al '14).

The take-away from this (perhaps an unfortunate figure of speech!) is that the odd doughnut or hamburger will not kill you if it is part of a really healthy diet. The problem, however, is that most of us live in a very toxic food universe.

“The odd doughnut or hamburger will not kill you if it's part of a really healthy diet. Polyphenols can help counter the increased cancer risk from deep-fried foods.”

NutriShield contains polyphenols (green tea, curcumin, grapeseed, bilberry) and **omega 3**.
nutrishield.com

ImmunoShield contains 1,3 1,6 beta glucans.
immunoshield.com

A supermarket ready-meal for one person of sweet and sour chicken and rice contained 10 teaspoons of sugar.

The Dr Paul Clayton Health Newsletter describes developments in the field of pharmaco-nutrition, where nature and science are combined to offer non-drug solutions to degenerative disease.

The newsletters are intended to increase knowledge and awareness of health issues and are for information only. No health claims for specific products are made or intended and the information should not be used as a substitute for medical advice.

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Fries or polyphenols contd

Take, for example, the shockingly high levels of **sugar** added to our foods. Recent surveys by *Which* magazine (Which '14) and *Action on Sugar* (AoS '14) found that most non-diet fizzy drinks exceed the WHO recommended levels for free sugars, and many own-brand ready meals contain roughly twice the recommended sugar levels. Sainsbury's sweet & sour chicken with rice and Tesco's Everyday Value sweet & sour chicken and rice contained 50.7g and 48.4g respectively – around ten teaspoons – in a meal for one; as do single serves of Old Jamaica Ginger Beer, Sainsbury's Cloudy Lemonade and many other carbonated drinks. (This is roughly twice the 25.5g found in a standard size bar of milk chocolate.)



If you're eating this much hidden sugar, then the likelihood of becoming overweight must increase, even as the nutrient density of the food you eat declines. This is a diet full of pro-inflammatory compounds and depleted in anti-inflammatory ones; and it is hardly surprising, given this food environment, that waves of obesity, chronic inflammation and chronic degenerative disease are swamping our ability to provide health care.

A new analysis has just found that the global number of overweight and obese individuals rocketed from 857 million in 1980 to **2.1 billion** (ie. a third of the world's

population) in 2013; that no country has successfully reduced obesity rates in 33 years; and that we are, as a species, getting fatter at a progressively younger age (Ng et al '14). Diabetes, cardiovascular disease, dementia and cancers inevitably follow in our increasingly broad wake.

Our toxic food universe forms the upper of a pair of millstones that is grinding us into disease and premature death.

The lower millstone is, of course, pharmaceutical medicine which is specific, expensive and very toxic (Starfield 2000). Seen in an historical perspective, modern medicine does little more than suppress the symptoms of diseases that have become rife due to our failure to maintain the lifestyles of our great-grandparents. This is why public health has become too expensive to continue in its present form, and too critical to be left to the medical profession.

Last year, WHO Director Margaret Chan called for the food industry to assume responsibility for its toxic products and either mend their ways or have mandatory health warnings stamped on their packs.

As part of the industry response, Tesco, the UK's largest food retailer, announced that they would ban sweets and chocolates from their checkouts. Not wanting to be vulnerable to any 'nanny state' arguments, they claimed that a survey of customers had showed overwhelming support for the ban. Frankly I don't care why they did it; it is a positive move.

The times may, at last, be changing.

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P3-4 Fries or polyphenols

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