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Ancient spice saves ageing nerves

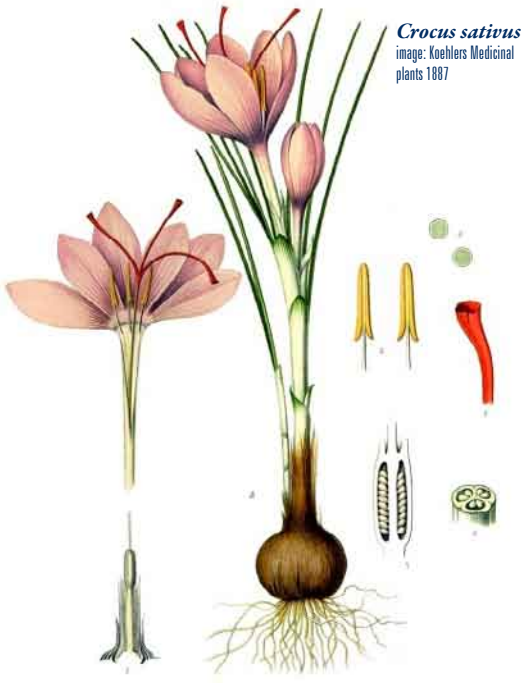
The aging of humans is one of the quiet revolutions of the 20th Century. Between palaeolithic (~2 million years ago) and modern times, the life expectancy of a newborn child remained fairly constant at less than 40 years (world-wild average) until in the last century, with the advent of modern medicine, this figure doubled to 60-70 years, exceeded 80 years in many societies, and continued to rise.

One of the many consequences of this quiet revolution has been the recognition of age-related diseases of the central nervous system (the brain and retina of the eye), conditions such as Alzheimer's dementia, Parkinson's disease, and age-related degeneration of the retina. All are becoming increasingly important, because the cohort of aged people is increasing faster than the population as a whole. They cause enormous human suffering, destroying the quality of the last decades of individual lives.

In devising potential therapies, medical scientists have essayed both the specific and general. For example, Alzheimer-like dementias, which are age-related, and insidious in their onset and progress, are associated with two types of proteins, so called amyloid and tau. These proteins are found either over-expressed (amyloid) or modified (tau) in the dementing brain, and are believed to hold the key to a cure. They have been isolated, sequenced, synthesized, genetically engineered and targeted with inventive therapies. Also, symptom-ameliorating drugs have been developed – the neurotransmitter dopamine in Parkinson's disease is perhaps the best known example. Yet, specific treatments able to prevent, stop or even delay the progress of the underlying pathology remain elusive.

As a consequence, other scientists have taken a quite different approach; if the diseases are age-related, then perhaps they can be treated as such. To do that, we need to recall why age-related diseases are so common in the aging brain and retina. The cells in our bloodstream are replenished hourly, those of our gut daily, which means they do not need to repair accumulated damage. By contrast, the nerve cells of the central nervous system, with very few exceptions, are serving a life-long sentence of hard labour. They are all generated before or soon after birth, and we need them to think and see and hear and drive our muscles for our lifetime. As they are not replaced, death of these cells during the course of our life may condemn us to permanent loss of our motor coordination and control, our memory and even our personality.

To achieve longevity, neurons do not stand stoically against the stresses of time, like a pyramid in the desert. To counter stress, nerve cells commit energy and complex, highly evolved mechanisms to the repair of their membranes, of the DNA in their chromosomes, and of their machinery, for example of the complex mechanisms of the mitochondria. How long they survive (hopefully a lifetime) depends on a balance between the stresses of time, and the ability of cells to self-repair.



Crocus sativus
image: Koehlers Medicinal plants 1887

The margin between death and survival may be small yet it follows the principle of financial survival of Dickens' Mr. Micawber: "Annual income twenty pounds, annual expenditure nineteen pounds nineteen shillings and sixpence, result happiness. Annual income twenty pounds, annual expenditure twenty pounds and sixpence, result misery".

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The question is whether the Micawber Principle also bears relevance for the survival of our nerve cells: Can the 'diseases' which result from stress-induced loss of nerve cells be prevented, delayed, slowed or even reversed by reducing, even if only slightly, the oxidative stress which afflicts all nerve cells as we age?

We are using an ancient spice, saffron, to do just that for the highly specialized photoreceptor cells of the retina. These are the neurons that detect light and transform its energy into the neural activity essential to vision; when they degenerate we go blind.

Saffron is working as a neuroprotectant, in animal models of retinal degeneration as well as in patients with age related macular degeneration. When we feed the animals with saffron, or give patients specially prepared saffron pills, the photoreceptors are more resistant to stress and, in humans, some recovery of function is apparent.

How does the saffron work? In Micawber's terms, we believe, it tilts

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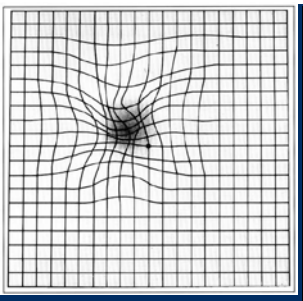
the fine balance between survival and death towards survival. In scientific terms, saffron is a powerful anti-oxidant – and oxidative damage has been identified as a factor in the instability and degeneration of photoreceptors.

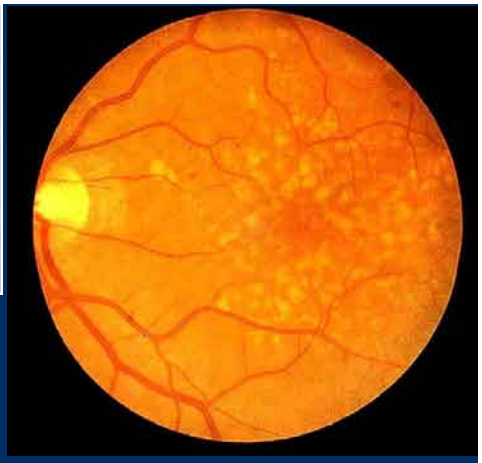
In the first phase of experimental work we found evidence of the neuroprotective potential of saffron, in a retina/light damage assay.

At this stage, we can say that dietary saffron shows intriguing promise as a retinal neuroprotectant, for patients with early AMD.

Saffron was an attractive candidate for testing, because the stigmata of *Crocus sativus* contain biologically high concentrations of powerful anti-oxidants (crocin, crocetin), whose multiple C=C bonds give the stigmata colour, fragrance, taste and anti-oxidant potential; and because of its centuries-long use as spice, with no known ill effects. Recently, we tested the 'medicinal' properties of saffron in a double-blind, clinical trial in patients with age-related macular degeneration (AMD).



Amsler grid as it might appear to someone with age-related macular degeneration.



Fundus photograph of a patient with age-related macular degeneration

images: National Institutes of Health

AMD is a major cause of loss of vision in older adults as the central region of the retina, which mediates high-resolution colour vision, degenerates selectively. Sufferers can't see detail, read or make out the faces of loved ones. AMD occurs in diverse forms, but a common feature is that the condition is progressive, and that recently introduced treatments provide some recovery of function.

In the damaged macula, therefore, it is possible that part of the loss of vision results from damage to (rather than death of) photoreceptors, the partial restoration of vision arising from cellular repair.

More generally, we have argued that damaged but repairable photoreceptors are present in many forms of retinal degeneration. Reducing oxidative stress on these damaged survivors may, we argue, allow the cells' self-repair mechanisms to rebuild the photoreceptors, restoring their specialized structure and mediating an increase in their responsiveness to light.

So we undertook an approved double-blind trial[1] of dietary saffron in human AMD), in which the principal outcome measures were the amplitude and phase of the focal (central 18°) electroretinogram (fERG) to 41 Hz flicker.

We found an increase in response amplitude, with a stable phase, indicating a recovery of retinal macular function (see figure 1). This effect was paralleled by an improvement in subjective visual acuity and reading vision. Sufferers regained some ability to read, and recognise faces. Recovery was never complete, and two of the many questions awaiting answers are how much recovery is possible, and how stable the recovery will be. At this stage, we can say that dietary saffron shows intriguing promise as a retinal neuroprotectant, for patients with early AMD.[2]

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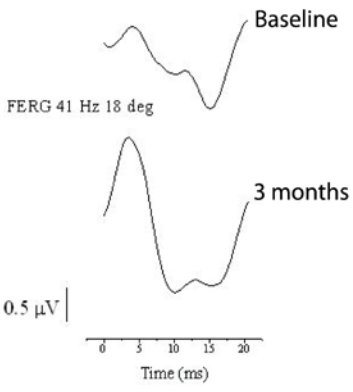
We are planning to replicate and extend our results in a cohort of AMD patients to be tested at the Save Sight Institute, Sydney University. We also plan to apply the same therapeutic approach in inherited retinal disorders having oxidative/light damage as a major underlying pathogenetic factor. Although we have been working with the neuroprotective effects of saffron for years now, it still seems remarkable that a common, mild spice can - in carefully designed experiments and trials - be so effective in preserving the nerve cells so important for normal life.



Focal electroretinogram changes following 3 months of Saffron supplementation in an AMD patient