Oxygen

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This is not a book on oxygen as a chemical element, nor is it a narrative of the prevalence of oxygen through geological times, although at times it promises to be either and both, but a book on ageing on the cellular level.

To start backwards, highlightening the main conclusion, to which the whole book is meant to strive. Ageing is due to the degeneration of mitochondria. And the clue to alleviate and postpone the inevitable conseqeunces of ageing, as sickness and ultimate death, is not to target each possible pathology that can arise, in particular the idea that the individual genom gives a blueprint for all the tribulations in store is misconceived, but to slow down the leaking of free radicals that is the side-effect of oxygenated metabolism.

In many ways there is nothing remarkable about the general tenor of such a proposal. After all ageing is just part of the general tendency for organisms as well as machines to wear down, articulated through the law of increasing entropy, that eventually will lead to the death of everything. In particular the human body is worn down, a process that is temporarily halted by its evolved ability to repair itself, but this very ability is part of the organism itself, and hence subjected to the same forces of wear down. Thus ageing becomes a vicious circle, as our ability to repair becomes impaired, thus making itself increasingly vulnerable to damage. This accounts for the accelerated process of ageing, through most of our lives we feel young and only marginally affected by age, and in fact most of the population needs very little medical attention, except at the very end of life. We all die of old age, and disease is just the opportunism of pathology enabled by an enfeebled body.

But it is one thing to talk in general philosophical terms about degeneration, quite another one to articulate it in precise ways, which after all is a prerequisite for our attempts to intervene in the process. Many scenarios have been proposed. One very popular a few years ago was in terms of telomere. It is observed that in the copying of DNA for technical reasons the ends are slightly chopped off, thus information is lost at each division. One may naively argue why division is possible after all, will not the cell become dysfunctional after just one division? The point is that the most of the DNA consists in 'rubbish' in the sense that it serves nu 'useful' function in the synthesis of proteins. This fact has troubled many biologists, but I think that there is no reason at all to be surprised. Why should the genetic program be 'edited' streamlined and ridded of redundancies? Who would do that editing? The basic principle in biology is whatever works, works, and if a lot of extraneous 'stuff' gets a free ride, so why not, at least as long as it does not interfere, in which case the main editor, in the shape of evolution, steps in. Now it turns out that the junk at the ends do serve a purpose, not one usually associated to the proper work of the DNA, but as a buffer. Thus in principle the longer the useless ends are, the more divisions the cell may experience. If the useless ends would be very long, we would in principle be able to live, if not for ever (because after all the length of a DNA molecule is bound to be finite) at least for very long. Ideally of course there would be no ends, the strains would be circular, and

nothing would ever be lost in principle at replication. The problem with this explanation is, the author points out, that first of all there is not much of a correlation between lengths of useless ends and longevity. The elephant, whose initial egg will have to divide many more times than that of a mouse, nevertheless has a much longer lifespan. Furthermore certain cells in the body does not divide, as the neurons of the brain, the muscles of the heart and skeleton, but those cells nevertheless age.

Oxygen so necessary for our life, whose deprivation, if only for a brief period, leads to suffocation and death, is nevertheless a poison. Strictly speaking, as the presence of aneorobic bacteria testifies, oxygen is not necessary for life in general, other pathways can be devised, is nevertheless extremly efficient. But aeorobic respiration produces free-radicals, like OH^-, which react with everything in sight, and more often than not release other free-radicals in the process starting a chain reaction. Such a state of affairs is a great threat to the integrity of the organism, and various stratagems for containing it has to be developed in order for it to work. So formidable is the task, according to the author, that all higher forms of life, starting with multi-cellarity, can be seen as an evolutionary response to the challenge. The author likens the production of free-radicals during oxygen-driven metabolism to the damage done by radiation, that likewise splits water molecules producing a spate of OH^-. One stratagem the body exploits, is to strictly limit the amount of oxygen that the cells have to handle, and to design various anti-oxidants that ameliorate the presence of free-radicals. (But the author points out that OH^- is so aggressive, 'attacking' everything in sight, that in order to neutralize it, there has to be such an overwhelming presence of anti-oxidants as to comprimise the necessary working of the cells.) This fact has led many people to advocate a dietary intake of anti-oxidants, vitamin C, being the prime choice (as exemplified by the strident advocacy of Pauling), with claims to the effect that massive doses of it, prevents from most ills. The author is rather sceptical about dietary supplements, the process being far too complicated as just being a matter of deficiency. For one thing, the body can only absorb so much vitamin C, any excess is execrated (thus in order to achieve the high levels necessary for clinical effects, doses have to be injected.) It is easy to imbue actors with intents, but vitamin C is only a 'good guy' under certain circumstances, if circumstances change it can as well have the opposite effect as a powerful pro-oxidizer. In fact the author speculates that the reluctance the organism exhibits in the absorption of vitamin C can have evolved as a defence mechanism. Sceptical as the author may be, he nevertheless points out that a rich intake of fruit and vegetables (he speaks about the necessary five portions a day) seems to have a beneficial effect, and is in fact being recommended by the health authorities. It could however be, that fresh fruit contains many other things, besides vitamin C, that can be the secret of its beneficial aspects.

The clue to metabolism is the motochondria. It is now generally believed that mitochondria should be considered as an independant organism from the cells themselves, they have in particular their own DNA, and the cells and the mitochondria have evolved a symbiotic relationship, in which their energyproduction is used by the cell, which in its turn may provide protection. The mitochondria being involved in the metabolism, becomes also the main source of free-radicals. Its DNA being unprotected, unlike that of the cell itself, it becomes particularly vulnerable to decay. As the mitochondria degenerates, it works less

efficiently, and also starts to leak out more free-radicals. To slow down the wear and tear one clearly would benefit from a slower metabolic rate, in particular a lower calorie-intake. And studies have shown that starved mice do indeed live longer. Also among mammals, life-spans differ wildly, although intrinsic life-spans in terms of heart-beats show a remarkable constancy. The number of heartbeats of an elephant and a mouse are roughly the same, also, due to the greater heatloss of small animals, the amount of oxygen consumed during a lifetime is also more or less comparable. Humans, for some reason stand above, being given a life-span in excess of its metabolic rate and number of heart-beats. Thus men live much longer than Chimpanzee and Gorillas. More interesting from a biological point of view, is that birds with very high metabolic rates have long life-spans. It turns out that their mitochondria is very effective, leaking very little free radicals. As the author notes, primary defences are superior to secondary. When free-radicals escape, you need to take care of them, which involves far more resources and energy and precision, than simply containing them at the source.

The genetic material in the cell is inherited half and half from each parent, while the mitochondria comes only from the mother[1]. There is a 'good reason' for this. As mitochondria replicates asexually, there is no possibility of rejuvenation through sexual recombination, also, as mitochondria are trapped inside cells, they cannot be selected for by the weeding out that affects bacteria rapidly increasing. Thus in order to have young mitochondria, available, it has to be 'deep frozen' in the sex-cells, as mitochondria that has divided a lot has degenerated[2]. The sperm contains just a few mitochondria, necessary for its propulsion, while the egg contains a lot in a virgin state so to speak. In this way the organism is assured of getting a supply of 'fresh' mitochondria. Incidentally this becomes the clue in distinguishing which is which of the two sexes of an organism. The male sex produces a lot of small disposable packages (sperms), while the female sex produces a few immobile big packages (eggs). In fact this illustrates that at least part of the homonocolus theory is correct, namely in a well-defined sense a part of you (your mitochondria) was part of your mother at her birth, and hence that of your maternal grandmother at her birth and so on. This also lends some confirmation to the observation that your health is more likely to be inherited from your mothers side than your fathers.

The process of ageing is now simply a fact of the degeneration of the mitochondria, leading to increased leakage of free-radicals that triggers the immune reaction, and thus submits your body to an unceasing activity of the former. Also, the immunesystem has no ulterior motives, it is not there to protect your body, it is just primed to work in certain ways. In your youth, its activities tend to be beneficial, as it leads to the destruction of invading bodies, and thus to inhibit the signals that triggered its activities in the first place. (Those signals essentially appears to be given by the free-radicals.) But when you are old, its activities are not regulated, the presence of the free-radicals are not due to anything that can be destroyed and expelled, and thus its activity is never inhibited.

This leads to some apparent paradoxes. Being of frail constitution in youth, may

[1] This maybe a slight exaggaration, it may be that the maternally inherited swaps the paternally

[2] In the case of cloning, like the famous sheep Dolly, this is not affected, and consequently the mitochondria is old, and the cloned individual ages quickly, in fact starting off at a later age than a new-born. This was illustrated by Dolly, which developed athritis at an earl age.

actually turn out to be a benefit in old age. Also the exposure to stresses in early infancy, may lead to a fine-tuning of the immunesystem. It is argued that the excessive cleanliness of modern society, is resonsible for the increased occurence of allergies and auto-immune diseases. The one gene of sicke-cell anemia does not give protection against malaria infection, but it suppresses the typical immune reaction to it, which is what makes the infection so dangerous in the first place. But of course there is a subtle balance between a strong immunesystem and a weak one. Suppress it, and the dangers of infections and cancers increase.

So what remedies does the author recommend? Naturally the time is premature for specific ones, except the usual guide-lines as to proper diet and exercise (always in moderation[3]) and the avoidance of various stresses. But in the long run therapies directly involving mitochondria seems to be the answer.

Initially the books promises to be a story of oxygen in a setting of natural history. Much interesting facts are to be gleaned from the first chapters. Perhaps the most striking one being that in former times the oxygen content in the air was in great excess of present levels. Some data points to values up to 35% in stead of 21% during the Carbontimes, and almost as high during the end of the Cretaceous. This would have enabled the development of large insects (as the giant dragonflies testify) and also resulted in large recurrent forest fires (the meteoric impact at the end of the Cretaceous may have caused world-wide fires, exacerbating greatly the catastrophic effects caused by the impact alone.). Such tremendous increases in the oxygenlevel must have been due to the large burying of organic material, removing it from the respitory cycle, thus leaving a surplus of oxygen from the photosynthetic process[4].

The author really takes the wide view, examining the role of oxygen in all possible aspects. He chimes medicine for being too little concered with theory and reflection, the extreme specialization of workers resulting in an overload of data. Science does not work through the compilation of data and the search for patterns, but through premeditated theories that guide you into what data to look for and test for corroboration or refutation. The world is too rich in facts to be systematically digested, we simply have to focus on its salient parts.

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[3] Gentle exercise stimulates replication of mitochondria, which will have the effect that healthy ones increase faster: while more vigorous create too much free-radicals. However no one knows where is the cut-off point

[4] This process cannot be continued indefinitely, as higher oxygen levels depress the photosynthetic process