Oxygen Homeostasis
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The Dysox Model of Aging

My grandfather forgot to die on time. We do not know how long he lived - 101 years, 102 years, or more. My grandmother was also a centenarian. With that genetic pool, I sometimes wonder about my own life span. Then I realize that my grandparents lived free of pesticides, refrigerators, and CNN. A large proportion of people of Hunza Valley and Okinawa Islands live for 110 or more years. When their children travel down to polluted plains of Pakistan or toxic cities of Japan in search of employment, they begin to fall prey to degenerative disorders within a decade or two. Their life span plummets. There is more to be learned about healthful aging there in my view, than in all the hopes and claims of enthusiasts of gene and 'longevity hormone' therapies. In this column, I look at old and new theories of aging through the prism of oxygen metabolism, and marshall evidence for my view that healthful human aging is, first and foremost, a matter of compromised oxygen homeostasis.

"The Aging Enigma: Scientists Probe the Genetic Basis of Longevity." That was the title of the cover story of Harvard Magazine of September 2005. That article included the following: "The experimental evidence that suggests that aging is under genetic control, rather than a consequence of normal wear and tear, is compelling." I do not share the author's excitement about that discovery. The language of genes is far too complex to accomodate that view of genomics. The issue is not that life can be extended by genetic modifications, but that the longer-living mutants show other serious effects - reduced fertility, developmental deformities, and others - a trade-off of uncertain values that is not likely to be acceptable to humans. Even when limited longevity advantages are realized through genetic modifications, I predict that those benefits will be drawn only to the degree that oxygen homeostasis of the subjects can be optimised. I return to this crucial subject later.

Some mechanically-oriented writers in the field of aging assert that what is required is a simple business plan for some grand spare parts relacement industry. One of them recently proclaimed: "It is only a matter of years - decades at most - until futuristic technologies will entirely reverse-engineer the human machine." He went on to prophesize "a radical life extension is close at hand." Such individuals seem not to see any differences between the precisely definable chemistry of inanimate materials and the ever-changing energetic-molecular kaleidoscopic mosaics of living beings. Some of them have pronounced aging to be disease, curable by nutritional and herbal products they sell. I do not share their enthusiasm either. The inter-relationships of ligands, receptors, biomembrane channels, protein pumps, and mediators of inflammation are far too intricate and labile to sustain those claims. Again, when limited longevity advantages are achieved through such 'reverse engineering,' I predict that those benefits will not last unless oxygen homeostasis can be preserved.

During the1930s, Clive McKay established that caloric restriction extends life span in many species. He implied that that is the only way of increasing the lifespan of mammals. Since that classic work, an enormous body of literature has accumulated validating the direct relationship between caloric restriction and longevity. This linkage has been documented in yeast, mosquitoes, flies, and rats. To cite a specific example, the life span of Saccharomyces cerevisiae increases by 25% when the glucose level in the culture is reduced from 2% to 0.5% Similarly, mosquitoes on caloric restrictions live longer than those with ad-lib (unrestricted) feeding.

In 1955, Johan Bjorksten proposed his cross-linking theory of aging. According to this theory, the basic aging process involves accumulation of disfigured and insoluble (cross-linked) proteins, DNA, fats, and other large-sized molecules, such as vitamin A. Simply stated, cross-linked molecules are two molecules wrapped around each other in such a way that neither can function normally. Such molecules cause aging by impeding or blocking the actions of redox-restorative and oxystatic substances - enzymes, antioxidants, and other nutrients. The process of cross-linking may be illustrated as follows: The structure of many healthy proteins resembles long threads of different sizes. Under heat or chemical stresses, individual molecules are bent, turned and twisted into many different shapes. Such misshapen molecules quickly regain their original shapes when the stresses subside. The term cross-linking means that such turned and twisted molecules get permanently disfigured because of excessive stress. Thus, such molecules are torn apart and,
when the ends unite, they get tangled with each other and form crooked protein molecules.

In 1956, Denham Harmon proposed his free radical theory of aging.\(^{12}\) According to this theory, the aging process involves molecular and cellular injury caused by free radicals. Free radicals are highly unstable, extremely reactive atoms or molecules that form during normal metabolism, as well as during cellular injury caused by chemicals, microbes, radiation, and other types of injury. Since its introduction, the basic tenet of this theory has been supported by an ever-growing body of data. Indeed, until recently, the case for this theory seemed iron-clad.

In 1962, Roy Walford put forth an immune theory of aging.\(^{13,14}\) He proposed that the aging process involves injury to the immune system of the body so that the immune system of a person becomes confused and turns against that person's tissues. Specifically, immune injury results in the production of abnormal antibodies that injure the body's own tissues rather than fighting microbes. Such antibodies are called autoantibodies.

### Aging and Rates of Auto-Oxidation and DNA Repair

The rates of spontaneous tissue breakdown generally correlate inversely with the species' life spans: the animal species with the highest rates of auto-oxidation have the shortest life spans, while those with the lowest rates of auto-oxidation have the longest life spans.\(^{15}\) Humans, with the lowest rate of tissue breakdown, has the highest longevity, while the mouse (which has the highest oxidation rate among the species listed in Table 1) has the lowest longevity. However, there are exceptions to that rule. For instance, mice and bats have similar metabolic rates, yet bats live nearly ten times longer than mice. It is also noteworthy in this context that antioxidant supplementation, in general, does not allow various species to live longer.

#### Table 1. Rates of Auto-Oxidation and Life Spans of Mammalian Species

<table>
<thead>
<tr>
<th>Species</th>
<th>Oxidation Rate</th>
<th>Life Span (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans</td>
<td>24</td>
<td>90</td>
</tr>
<tr>
<td>Orangutan</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Baboon</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Green monkey</td>
<td>41</td>
<td>34</td>
</tr>
<tr>
<td>Squirrel monkey</td>
<td>74</td>
<td>18</td>
</tr>
<tr>
<td>Rat</td>
<td>104</td>
<td>4</td>
</tr>
<tr>
<td>Mouse</td>
<td>182</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Deoxyribonucleic acid in cells is under unrelenting assault from disruptive influences. Fidelity in its structure and during its duplication is evidently crucial to cellular structural and functional integrity. That is assured by a stunning array of cellular enzymes that detect and repair deletions, additions, and translocations in DNA threads. Such enzymes not only remove damaged segments, but also rapidly reconstitute the DNA threads in areas of gaps left by the damaging agents. The functionalities of such enzymes diminish with age. The efficiency of DNA repair enzymes can be assessed by measuring the rate of consumption of such enzymes added to DNA damaged under control conditions (in which nucleotides are exposed to various DNA-damaging agents).

In 1973, Hart and Setlow measured rates of DNA repair in fibroblasts from a number of species and plotted it as a function of the maximum life span of the species.\(^{16}\) Table 2 shows data for humans, Indian elephant, cow, golden hamster, Norwegian rat, field mouse, and long-tailed shrew. The numbers have been rounded to simplify the presentation of data.

In 1983, I put forth my spontaneity of oxidation (SO) model of aging.\(^{17}\) This model holds that aging involves loss of energy triggered, perpetuated, and completed by the ongoing and spontaneous loss of electrons in the body. Even a cursory look at the cross-linkage, free radical, and immune theories makes it clear that the SO model is fully consistent with all three. Indeed, my model then represented an extension of those theories in the sense that it provides a clear underlying mechanism for all three. A large body of data is summarized in Tables 1 and 2 to validate the various aspects of the SO model of aging.

#### Table 2. DNA Repair as a Function of Life Span*

<table>
<thead>
<tr>
<th>Species</th>
<th>DNA Repair (relative)</th>
<th>Life Span (logarithm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Indian elephant</td>
<td>4.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Cow</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>Golden hamster</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>Norwegian rat</td>
<td>1.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Field mouse</td>
<td>0.8</td>
<td>0.38</td>
</tr>
<tr>
<td>Long-tailed shrew</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* All values are included as close approximations for the sake of simplicity.
** Life span is given as logarithmic value of the maximum species life span.

In 1996, Cynthia Kenyon demonstrated that *C. elegans* round worm missing one copy of daf-2 gene 'stop the clock' by becoming dauers, assume a spore-like state akin to hibernation, and can live for long periods of time.\(^{18,19}\) She deduced from her observations that the program that controls longevity in that worm can be uncoupled from other physiological processes. In that year, Guy Ruvkun extended Kenyon's observations by showing that daf-2 and age-1 genes were part of the same genetic/molecular pathway, and that daf-2 encodes an insulin receptor, thus linking aging to insulin signalling and to McKay's observations concerning the extension of life span with caloric restriction.\(^{20,21}\)

During the late 1990s, Leonard Guarente and David Sinclair examined the mechanisms of aging in yeast cells that divide an average of 20 times - 40 times at most - and showed that the life span of yeast can be extended when its DNA is stabilized (rearrangements are prevented).\(^{22,23}\) Specifically, the yeast live about 30% longer when an extra copy of Sir2 gene is inserted in it to stabilize its DNA. The Sir2 gene is considered to be the founding member of the family of genes that encode sirtuins, proteins that evolved about a billion years ago to preserve the life span of various species during periods of stress. PNC1 is another gene designated as the 'master regulator' that regulates Sir2, of importance in this context. It has also been shown that the levels of SIRT1 (the mammalian equivalent of Sir2 in yeast) rise when the levels of insulin and IGF-1 fall during caloric restriction.

Sinclair then claimed he had identified certain plant molecules that can activate the Sir2 protein, designated...
**Dysox Model of Aging**

sirtuin activating compounds, or STACs with life extension benefits. Resveratrol, of no proven value for human life extension so far, is one such STAC that excites the practitioners of the anti-aging industry. Sirtuins are considered to be controlled by insulin and insulin-like growth factor-1 (IGF-1).

The Sir2 family of regulatory proteins has important regulatory roles in aging. Specifically, this family links chromatin silencing, metabolism, and aging. In yeast aging and most likely in aging of many other species, the chromatin silencing functions are critical to life extension. Caloric extension increases the activity of Sir2. Some members of this family function as longevity proteins with transcriptional silencing ability. The silencing protein Sir2 and its homologs are NAD-dependent protein deacetylases. Sir2 protein and its homologs contain a phylogenetically conserved NAD-dependent protein deacetylase activity. The Sir2/3/4 complex and Sir2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. Sir2 proteins also have a well-delineated role in life extension by calorie restriction in *Saccharomyces cerevisiae*. The effect of caloric restriction in this context also requires the role of nicotinamide adenine dinucleotide (NAD).

**Genetic Modifications and Aging**

During the last two decades, remarkable advances in the genetics of aging occurred. Most notable among them, in addition to the Sir2 family of genes, are genes of Hap4 Transcription Factor, HXK2, daf-2, age-1, and cytochrome c1 (CYT1) groups.

HXK2 is another gene of importance. It encodes one of the three hexokinases that introduce glucose into glycolysis.

It was expected to mimic the effects of growth in low-glucose medium, which it did. HXK2 deletion is known to extend life. Interestingly, that deletion was found to also increase respiration. Transcriptional profiling of *S. cerevisiae* genome disclosed a highly significant overlap in the transcriptional changes induced by low glucose (0.5%) growth and that seen with HXK2 deletion. Hap4 transcription factor activates many genes involved with mitochondrial respiration. Transcriptional profiling reveals that many of those genes, upregulated more than two-fold by Hap4, are involved in the metabolic switch from fermentation to respiration. In *S. cerevisiae* life extension studies, overexpression of Hap4 redirects the respirato-fermentative flux distribution, resulting in a switch of metabolism from fermentation toward respiration, and provides further direct evidence for the pivotal role of oxygen in aging. Cytochrome C1 is the protein involved with electron transport in *S. cerevisiae*. The life span of some yeast strains can be extended under certain conditions. Deletion of the gene encoding cytochrome c1 (CYT1) abrogates life extension under those conditions, supporting the view that metabolic shift to respiratory ATP production is a pre-requisite for life extension under experimental conditions.

**Respiratory-to-Fermentative Shift and Aging**

In 1998, I introduced the term *dysoxygenosis* for a state of partial or complete failure of oxygen utilization in cells. I put forth the hypothesis that dysoxygenosis is caused by impaired function of enzymes involved in oxygen homeostasis ("oxyenzymes") and leads to altered expressions of genes induced by hypoxic environment ("oxygenes"). The webs of oxyenzymes are vast, with each entity linked to every other through multiple pathways. The webs of oxygenes are seemingly far more complex. All such webs are exquisitely "aware" of changes in oxygen availability in their microenvironment and vigorously respond to them. When one thing changes in those webs in one way, everything changes in some way. Dysoxygenosis, then, is discerned as a state caused by a rich diversity of elements but one that creates the same cellular oxygen dysfunction. In 1998, I also introduced the terms *dysfunctional oxygen metabolism* and *oxygen disorder* for readers without medical or biochemical background.

In 2000 in *Oxygen and Aging*, I presented my oxidative-dysoxygenative model of aging, as an extension of the earlier SO model of aging. Simply stated, that theory holds that within the confines of genetic limits, the primary aging process involves dysoxygenosis. In that state, the cells, tissues, and body organs age because they cannot maintain oxygen homeostasis. The essential difference between the 1983 and 2000 models is this: In the former, the focus was essentially on the primal oxidative drive provided by spontaneity of oxidation in nature and the degradative consequences of free radical generation triggered, amplified, and perpetuated by the phenomenon; by contrast, the emphasis in the oxidative-dysoxygenative model is on both the regenerative and degradative aspects of oxygen homeostasis and of oxygen-related factors.

During the early years of this century, Lloyd Demetrius put forth his metabolic stability hypothesis of aging holding that the length of life span is determined by the stability of free radical activity. The proposed mechanism in this model is based on the hypothesis that metabolic stability — the capacity of an organism to maintain steady state values of redox couples — is a prime determinant of longevity. It integrates a molecular model of metabolic activity (quantum metabolism) with an entropic theory of evolutionary change (directionality theory) to propose a proximate mechanism and an evolutionary rationale for aging. The mechanistic aspects of this model are used to predict that caloric restriction extends life span by increasing metabolic stability. The evolutionary aspect is used to predict that the observed increased longevity with caloric restriction in rats will not hold for primates. That is because rats show early sexual maturity, a narrow reproductive span and a large litter size, all three features indicating low entropy. This model then holds that Darwinian fitness in the mouse derives from its metabolic flexibility, whereas such fitness in humans relates to their physical robustness, and dashes the hopes of those who undertake severe caloric restriction in order to live longer.

**Insulin Signaling and Aging**

In 1997, Gary Ruvkin showed that *daf-2* encodes an insulin receptor. His landmark studies firmly established the link between aging and caloric restriction in roundworms. That also raised some important questions. Could an experimental model be generated in which the animal eats more, weighs less, and lives longer? Since insulin signaling is clearly involved with the current epidemic of obesity, and presumably reduced life span, could such animal model be produced by genetic modification of insulin signaling? In fruit
flies and roundworms, the same protein serves as the receptor for insulin and growth hormone. Could that knowledge be of value in constructing the desired animal model? To pursue those questions, C. Ronald Kahn generated mutant mice with genetically knocked out insulin signaling.44

Specifically, he generated fat cell insulin receptor to knockout mice (FIRKO mice), the muscle cell insulin receptor knockout (MIRKO) mice, the liver cell insulin receptor knockout (LIRKO) mice, and the neuron insulin receptor knockout (NIRKO) mice. FIRKO, MIRKO, and LIRKO mice are metabolically inefficient. The FIRKO mice turned out to eat more, weigh less, and live longer. Interestingly, these mice showed no change in the level of sirtuin proteins in their fat. I might point out here that there is decreased expression of several genes involved with mitochondrial oxidative phosphorylation, as well as changes in the levels and ratio (NAD/NADH) of crucial metabolites. The observations with FIRKO, MIRKO, and LIRKO mice have so far not provided clear answers as to the essential nature of the aging process; however, those findings do shed some light on the dysox model of aging as discussed below.

In human biology, mitochondrial respiration energetics produce ATP from ADP phosphorylation, and the electron transport in that process accounts for most reactive oxygen species (ROS) production.45

ROS generation begins with molecular oxygen picking up electrons to produce superoxide at complex I and III.47 Located at the inner mitochondrial membrane are anion transporters called uncoupling proteins (UCP-1, UCP-2, and UCP-3), which permit proton leakage back into the mitochondrial matrix, two consequences of which are a decrease in the potential energy available for ADP phosphorylation and a reduction in ROS generation. UCPs also increase respiration, which accelerates superoxide production in the setting of low protonmotive force.48 Superoxide, in turn, activates uncoupling protein. Thus is established a valuable contrariety which accelerates superoxide production in the setting of low levels of molecular energetics of human biology.

In the vascular wall, smooth muscle cells are the principal source of ROS.49 For studying the effects of uncoupling respiration and oxidative phosphorylation, mice with doxycycline-inducible expression of UCP1 restricted to aortic smooth muscle cells were generated. In mice given doxycycline (2 mg/ml in sucrose-containing drinking water), aortic UCP-1 messenger RNA expression was induced by nearly 12-fold compared with mice drinking sucrose-containing water alone.50 Doxycycline induction of aortic UCP-1 expression significantly increases both systolic and diastolic blood pressure. That hypertensive effect was abrogated 10 days after removing doxycycline from the drinking water. Plasma renin activity also increases significantly—up to threefold—in doxycycline-treated mice. Concomitantly, urinary sodium excretion decreases in the presence of doxycycline, suggesting activation of the renin-angiotensin-aldosterone system. By contrast, urinary excretion of norepinephrine, a marker of sympathetic activation, is not altered by UCP1 induction.

The Dysox Model of Aging

Models in medicine are proposed for two primary reasons: (1) for their power to bring together seemingly disparate findings to make a meaningful whole; and (2) to provide scientific rationale and/or basis for designing strategies for meaningful interventions. The dysox model of aging, in my view, has enormous explanatory power for nearly all, if not all, clinical, epidemiologic, and experimental observations concerning the aging processes in humans as well animal aging models. McKay's caloric restriction extends life span because it reduces the total burden on oxygen homeostatic mechanisms. The same holds for Bjorksten's cross-linking, Harmon's free radicals, and Demetrius' metabolic stabilities theories. The dysox model also provides the thread that binds Kenyon's observations with C. elegans, Ruvkin's linking ofdaf-2 with insulin signaling, Guarente and Sinclair's findings with Sir2, and works of others with HXX2, Hap4, cyclochrome C1, superoxide genes. Finally, and most importantly, the dysox model of aging is supported by the recent work that established that atherosclerosis results from uncoupling of respiratory chain complexes from oxidative phosphorylation. Clearly, one cannot separate the aging process among humans without considering the clinical consequences of common degenerative disorders, such as cardiovascular lesions, obesity, diabetes, and neurodegenerative disorders.

As for designing intelligent interventional strategies, the dysox model of aging clearly shifts the focus from the dynamics of individual genes to a holistic view of the three primary regulatory mechanisms of the body: oxygen homeostasis, redox equilibrium, and acid-base balance. For addressing those issues, I employ the Sun-Soil Model of the health/dis-ease/continue continuum. The Sun in that model symbolizes a person's spiritual belief in the healing dynamics, whereas the soil is represented by ecologic dynamics and inter-relationships among the bowel, blood, and liver ecosystems. The Sun-Soil Model of health and healing has been described at length in Integrative Nutritional Medicine, the fifth volume of The Principles and Practice of Integrative Medicine.51 The various aspects of that model are addressed at length by other contributors to this special Townsend issue on aging.

References

6. Roth GS, Ingram D K, Lane MA. Calorie restriction in primates: will it work and how will we know? J, Am. Geriatr. Soc. 1999;47:996-993

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