The nature of aging.

Part I: Aging

Every one desires to live long, but no one would be old.
- Jonathan Swift (1667-1745), Thoughts on Various Subjects, Moral and Diverting [1]

To lengthen thy life, lessen thy meals.
- Benjamin Franklin, Poor Richard's Almanack, June 1733 [2]

Calories are a primary cause of aging, and ***the*** limiting factor in lifespan.
Key insight: cutting calories slows the aging process and prolongs life.

Aging is due to a combination of years of age and total calories eaten in your lifetime.[3]
The road to aging is paved with calories.
The simplest way to reduce calories is to reduce portion size: use a small plate!

By my calculations, **every calorie above the absolute minimum *ages your body and your mind* and hastens death by about 31 seconds** (+/- 10). This means that you age one day (and lose one day of life span) for every 2800 calories you eat - above a starvation diet with good nutrition (adequate protein, fats, vitamins and minerals). Carrying an extra pound of weight for one year costs 2 days of life span. In dollar terms, a candy bar might cost $20 in potential lost wages. (See "Effect of CR.XLS" for calculation details). A 40-year-old man can live 8 years longer by eating 25% less; a 15-year-old can live 16 years longer by eating 25% less. Slowing aging means MORE YOUTH, not more old age.

Turn this around: it is VERY expensive – in terms of money, aging, disability and early death – to keep your weight up!
Can **you** afford to stay plump?

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Part I. What is aging?

Aging is not just a property of life: it happens to inanimate objects such as houses and cars. Even the soil in our yard is made of decomposed granite, the result of aging effects on this very hard rock. In some ways, "aging" seems to be a term for describing the increasing disorder that comes with time. On a low level, "Aging is a stochastic [random] process that occurs after reproductive maturation and results from increasing systemic molecular disorder. This disorder has multiple etiologies, including damage by reactive oxygen species, but generally from the diminishing loss of energy states necessary to maintain molecular fidelity."[4] At first glance, aging on a gross scale is something we all "know", but stating the properties of aging is useful. In animals and man, aging takes place on many levels. The following is my own listing in approximate order from large to small. Many span several levels and are in turn influenced by other aging processes.

1. **Whole body**
    a. Gross injuries: broken bones, auto accidents, war wounds.
    b. Loss of hormone regulation
2. **Organ**
    a. Gradual accumulation of damage to various parts of the body from infection, inflammation, cavities, surgery, etc.
    b. Increasing blood vessel damage: atherosclerosis leading to dementia, heart failure, heart attacks and stroke.
    c. Ever-accumulating incidence of certain catastrophic diseases such as cancer, multiple sclerosis, stroke and heart attack. In turn, the incidence of these diseases is influenced by various risk factors including genome and exposure to toxins.
    d. Gradual loss of the youthful structure and composition of various organs such as muscle and skin.
    e. Loss of the stem cell population
    f. Sarcopenia
    g. Osteoporosis & arthritis

h. Loss of insulin sensitivity

3. **Cell**
    a. Limitations on cell replication (perhaps related to telomeres).
    b. Accumulation of waste.
    c. Accumulation of toxins.
    d. Failure of mitochondria from accumulation of reactive oxygen species-induced damage to its DNA and membranes.
4. **Molecule**
    a. Damage to the body's proteins: glycation leading to AGEs (Advanced Glycation End-products = sugar-protein molecular bonds that have reached a stage that is difficult for the body to eliminate**)**, ultraviolet damage from the sun, calcification of blood vessels, other chemical reactions.
    b. Free radical damage to many classes of molecules, including proteins, membrane lipids and DNA. This is especially important in mitochondria, where perhaps 90% of the free radicals in the body are formed - and react.
    c. Random breakdown of the organic molecules that make up our body, through chemical reactions, natural radiation effects, etc.
    d. Intracellular damage to nuclear and mitochondrial DNA.
    e. Changes in DNA hypomethylation.[5]

Certain other things occur with age, but I do not think they are necessarily part of the aging process per se:

1. Natural changes with time such as sexual maturation, male baldness and presbyopia. For example, presbyopia probably results from the ever-increasing size and stiffness of the lens.
2. Hormonal changes: decreased growth hormone levels in the 40's, menopause.

Virtually all aging effects can cause loss of function or death. If you drink from the fountain of youth in the morning and die in an auto accident that night you have gained nothing. Sorting through which of these is most important is challenging; but it appears that mitochondria damage is the most important cause of aging, and cardiovascular disease is the largest apparent cause of death and disability. Caloric restriction (CR = eating less) with optimal nutrition (ON) is the most effective way to reduce both of these.

One interesting part of aging in living organisms is its dapple nature. "One of the most characteristic and widely observable features of senescence, usually ignored by scientific investigation, is a very variable, dapple distribution of its manifestations, seen within systems, organs, and tissues of the same individual. Different parts of an organ or tissue undergo senescence at different ages. … The results of the interpretation allow us to suppose that different parts of a human body usually have unequal genetic limits of life duration and their own programs of ageing; each of them has its own 'biological watch' which tells a different time. The genesis of this diversity can be explained by hybridization of persons with different genetic susceptibility to internal and/or environmental factors inducing senescence." [6]

Aubrey de Grey (Cambridge University aging theorist) has started an effort to "cure aging", SENS (Strategies for Engineered Negligible Senescence). He has identified seven aging processes that he thinks are critical:[7]

1. Cell loss & atrophy
2. Nuclear mutations.
3. Mitochondrial mutations
4. Death-resistant cells
5. Extracellular cross-links (AGEs)
6. Extracellular junk (e.g., in Alzheimer disease)
7. Intracellular (lysosomal) junk

Part II: Aging markers

People clearly recognize external signs of aging in other people: such as gray hair, wrinkles, and slowness of thought. It may be useful to recognize other markers that could be used to help assess whether an intervention slows the aging process. For example, using this approach, CR slows the onset of most of these markers (below):

1. **Whole body.** There are some grossly obvious aging biomarkers: wrinkles, arthritis, mental slowing, failure of the senses, and increasing rate of many diseases.
2. **Organ.** The following are associated with aging on the organ level.[8]

Loss of structure and function in aging.
Figures represent percentage of a given function remaining in an average 75-year-old man compared with that found in an average 30-year-old man, the latter value taken as 100%.

Weight of brain	56%
Blood supply to brain	80
Output of heart at rest	70
Number of glomeruli in kidney	56
Glomerular filtration rate	69
Speed of return to normal pH of blood after displacement	17
Number of taste buds	36
Vital capacity	56
Strength of hand grip	55
Maximum O_2 uptake during exercise	40
Number of axons in spinal nerve	63
Velocity of nerve impulse	90

3. **Cell** [9]
   - Mitochondrial damage (reduced by CR)
     - DNA mutations accumulate
     - Increased production of reactive oxygen species (ROS, e.g. H_2O_2 and $O_2^{\cdot}$-)
     - Decreased level of cardiolipin (reversed by acetyl-L-carnitine)
     - Decreased inner membrane potential (less efficient production of ATP for use by the cell)
     - Reduced cytochrome c oxidase activity
   - Increased susceptibility to oxidative stress
   - Shortening of the telomeres and failure of cell division
3. **Molecule** [10]
   - Accumulation of advanced glycation end-products (AGEs; reduced by CR and by reducing intake of food with high glycemic index, and perhaps reduced by certain supplements)
   - Accumulation nuclear DNA damage
   - Accumulation of oxidized proteins (some inactive, some cross-linked and thus "stiff")
   - Accumulation of oxidized lipids
   - Accumulation of lipofuscin
   - Accumulation of toxins such as heavy metals

Part III: Theory

I like to divide aging theory into two somewhat related categories: A) Mitochondrial damage and B) Entropy. Any theory of aging has to account for the profound beneficial effects of caloric restriction: mitochondria damage theory does this best, as best I can tell (glycation also works to a limited degree).

There are other theoretical mechanisms of aging, having to do with telomere damage, the effects of insulin (mediated by mitochondria free radical production[11] [12]), IGF-1 (insulin-like growth factor), Sir2, heat-shock protein etc. However, to me they seem to be relatively less important, are positively affected by the same things that prevent mitochondria damage, are less studied or studied only in lower organisms (yeast and nematodes); at this time I do not see a way to personally make constructive use of these theories. Note: reduced accumulation of toxins such as Advanced Glycation End-products (AGEs) can also account for *some* of the beneficial effects of CR.

See also the SENS website[13] for a list of the seven (and only seven!) major categories of age-related damage that result in the aging process.

A) **Mitochondria theory**

The mitochondria are where nearly all of our useable energy comes from: they take the food we eat (in the form of glucose, protein, fats & alcohol) and convert it to useable energy in the form of ATP. Damage to mitochondria DNA and membranes occurs with age, resulting in some mitochondria which lose oxidative phosphorylation capacity. Unexpectedly, these defective mitochondria become dominant in a small number of postmitotic cells (e.g., brain and muscle), and these cells spew out toxic superoxide .

A recent theoretical study of the effects of free radical damage to mitochondria showed that these effects alone can account for most of the properties of aging (gradual loss of function, the mortality curve, and the effect of CR).[14] In essence, reduction of mitochondria damage is the bottleneck in reducing aging (but see de Grey's hypothesis below).

A study in Nature (May 27, 2004)[15] found a causative link between progressively increasing mitochondria DNA defects and aging. The authors engineered a mouse with defective mitochondria DNA polymerase. Over time, the mitochondria in the mice had increasing defects: "This increase in somatic mtDNA mutations is associated with reduced lifespan and premature onset of ageing-related phenotypes such as weight loss, reduced subcutaneous fat, alopecia (hair loss), kyphosis (curvature of the spine), osteoporosis, anaemia, reduced fertility and heart enlargement. Our results thus provide a causative link between mtDNA mutations and ageing phenotypes in mammals." These same progressive mitochondria defects occur with age in normal mice and men, and are directly related to caloric intake. Also see Science 2005[16]. As I understand it, the calories are "burned" in the mitochondria => free radical damage to the mitochondria inner membrane & mtDNA. Common antioxidants such as vitamins E & C do not affect this process.

A 2005study in Science found that mice that made more catalase in the mitochondria lived about 20 percent longer; "These results support the free radical theory of aging and reinforce the importance of mitochondria as a source of these radicals." [17]

Mitochondria are the main source for useful energy in all eukaryotic cells (e.g., the cells in all animals): this is where the metabolism of fats and glucose takes place. This is also where the large majority of free radicals are generated, slowly causing damage and eventual failure. Mitochondrial damage *may* be the main cause of aging and death, anything protects mitochondria may slow the aging process. This damage seems to come from damage to the inner membranes, from DNA damage ("Because mitochondrial DNA, which is essential for execution of normal oxidative phosphorylation, is located in proximity to the ROS-generating respiratory chain, it is more oxidatively damaged than is nuclear DNA. Cumulative damage of mitochondrial DNA is implicated in the aging process and in the progression of such common diseases as diabetes, cancer, and heart failure."[18] [19]), or both. There are a few things that *may* reduce the rate of this metabolic damage: caloric restriction, R(+) alpha lipoic acid, limiting polyunsaturated fatty acids (DHA from fish), and avoiding ultraviolet-A (sunlight) exposure. It has been shown that "Mitochondrial membrane peroxidizability index is inversely related to maximum life span in mammals", with long-lived animals having less DHA in the mitochondria membranes.[20] (Parenthetically, a special and expensive form lecithin (that is not available for supplement purchase) may reduce mitochondrial DNA damage[21]: if so this one fact alone may be of great importance in reducing the rate of aging.) This is all promising, but unproven. (see Michael Rae's discussion[22], and Aubrey de Grey's discussion on PDF[23])

I think the following abstract is worth quoting in its entirety[24]:

> "**Available studies are consistent with the possibility that oxygen radicals endogenously produced by mitochondria are causally involved in the determination of the rate of aging in homeothermic vertebrates**. Oxidative damage to tissue macromolecules seems to increase during aging. The rate of mitochondrial oxygen radical generation of post-mitotic tissues is negatively correlated with animal longevity. In agreement with this, long-lived animals show lower levels of oxidative damage in their mitochondrial DNA (mtDNA) than short-lived ones, whereas this does not occur in nuclear DNA (nDNA). **Caloric restriction, which decreases the rate of aging, also decreases mitochondrial oxygen radical generation and oxidative damage to mitochondrial DNA**. This decrease in free radical generation occurs in complex I and is due to a decrease in the degree of electronic reduction of the complex I free radical generator, similarly to what has been described in various cases in long-lived animals. These results suggest that similar mechanisms have been used to extend longevity through decreases in oxidative stress in caloric restriction and during the evolution of species with different longevities."

Aubrey de Grey's hypothesis is based on the fact that there are a small number (<1%) of post-mitotic cells, that gradually increase in time, which change their oxidative mechanism and spew out superoxide. This toxic superoxide then causes widespread damage. As best I can tell, his hypothesis is well based and well thought out, fits with known data, and has yet to be seriously challenged, unlike several other mitochondrial

damage hypotheses.

B) Entropy.

Reliability theory / Systems redundancy. This theory points out that aging and death are direct and inevitable consequences of systems redundancy.[25] [26]

> Reliability theory is a general theory about systems failure. It allows researchers to predict the age-related failure kinetics for a system of given architecture (reliability structure) and given reliability of its components. Reliability theory predicts that even those systems that are entirely composed of non-aging elements (with a constant failure rate) will nevertheless deteriorate (fail more often) with age, if these systems are redundant in irreplaceable elements. Aging, therefore, is a direct consequence of systems redundancy. Reliability theory also predicts the late-life mortality deceleration with subsequent leveling-off, as well as the late-life mortality plateaus, as an inevitable consequence of redundancy exhaustion at extreme old ages. The theory explains why mortality rates increase exponentially with age (the Gompertz law) in many species, by taking into account the initial flaws (defects) in newly formed systems. It also explains why organisms "prefer" to die according to the Gompertz law, while technical devices usually fail according to the Weibull (power) law. Theoretical conditions are specified when organisms die according to the Weibull law: organisms should be relatively free of initial flaws and defects. The theory makes it possible to find a general failure law applicable to all adult and extreme old ages, where the Gompertz and the Weibull laws are just special cases of this more general failure law. The theory explains why relative differences in mortality rates of compared populations (within a given species) vanish with age, and mortality convergence is observed due to the exhaustion of initial differences in redundancy levels. Overall, reliability theory has an amazing predictive and explanatory power with a few, very general and realistic assumptions. Therefore, reliability theory seems to be a promising approach for developing a comprehensive theory of aging and longevity integrating mathematical methods with specific biological knowledge.

I think this theory is at least partially correct. Another way of putting it is that we get frailer with age.

Complexity theory explains the frailty that comes with age as a loss of complexity[27] (similar to failure of parts of redundant systems). As I interpret it this is another way of stating the Systems Redundancy theory.

Mortality doubling time can be thought of as inversely related to the "rate of aging" for a species; e.g., baboons mortality doubling time is smaller (3.5 yr doubling time in the wild) than that of people (7-9 yr), so they die sooner.[28] Why does his matter? Because an intervention that eliminates a prominent cause of death at a certain age (e.g. breast cancer in women less than 60 yr) but does not change the mortality doubling time will have an insignificant effect on prolonging life, while an intervention such as CR that lengthens this doubling time will have a substantial effect.

Part IV: Interventions

Mitochondria damage theory implies that the single most important factor in slowing aging is caloric restriction, and that this is the over-riding factor in helping to prolong life as well. Systems redundancy & complexity theories imply that the approach to health should be multi-factorial.

I think one should seek to improve health in as many ways as are reasonable (caloric restriction, avoiding advanced glycosylation end-products, reduction of specific disabling and deadly diseases such as Alzheimer's & cardiovascular disease, safety, exercise, avoidance of toxins such as tobacco and partially hydrogenated (trans-) fats, proper diet, avoiding sunlight damage etc.) On the other hand, figuring out what interventions make a worthwhile difference takes the carefully considered application of lab and clinical science. The results of this research are what make up the documents "3 CR.doc" and "4 Diet specifics.doc".

Do interventions work in people? See the other documents for the details, but in brief the answer is yes, to a large degree. My guess is that a person who started the primary interventions in middle age (35-45 yr) could add perhaps 10 years of useful lifespan and reduced aging, while a person who started in early youth could add perhaps 20 years. A study of 7th Day Adventists in California estimated that "Choices regarding diet, exercise, cigarette smoking, [and] body weight …, in combination, appear to change life expectancy by [up to ten] years."[29] Another study showed that those people with few "life style-related risk factors, including cigarette smoking, physical inactivity, and under- or overweight" had fewer disabilities until just at the end of life. "**The risk-factor-free group showed average disability scores near zero 10-12 years before death, rising slowly over time, without evidence of accelerated functional decline. In contrast, those with two or more factors maintained a greater level of**

disability throughout follow-up and experienced an increase in the rate of decline 1.5 years prior to death. For those at moderate risk, the rate of decline increased significantly only in the last 3 months of life."[30] I interpret this as showing that you can prevent age-associated disability by taking care of yourself.

There is also theoretical reason to think that these interventions should start as early in life as possible: "**even small progress in optimizing the early-developmental processes can potentially result in a remarkable prevention of many diseases in later life, postponement of aging-related morbidity and mortality, and significant extension of healthy life span.**"[31]

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