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TWO CERTAINTIES OF LIFE

NO NEW TAXES!

HERE LIES EVERYONE
250,000 BC - 2110 AD
Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death.
ARE AGEING AND DEATH INEVITABLE?
HOW OLD CAN ONE GET?

A Great Basin Bristlecone Pine forest

*Pinus longaeva*
Long-lived aquatic animals

White sturgeon
>100 years

Black coral colony
around 4,000 years old

Turritopsis dohrnii
the immortal jellyfish
Aldabra Giant Tortoise
*Geochelone gigantea*

Highest recorded life span of 255 years
Terrestrial animals

The maximum age a species, including humans, can reach depends on both biology (simpler organisms can reach Methuselah ages that more complex creatures cannot) and environment (dangerous surroundings lead to evolution of rapid reproduction, fast aging and early death).

Maximum recorded life spans (years, in wild):
- Dragonfly (4 months)
- House mouse (1 year)
- Jackrabbit (13 years)
- Rabbit (4 years)
- Dog (29 years)
- Cat (36 years)
- Bat (30 years)
- Condor (75 years)
- Horse (62 years)
- Chimpanzee (59 years)
- Queen termite (50 years)

Scientific American Sep 2010
An adult salamander

*Msx1* to the Rescue
Honey bee castes have different lifespans even though a queen or a worker can be formed from the same egg.
Madame Jeanne Calment of Arles, France, photographed in 1994 at the age of 119. She died in 1997, aged 122, of ‘natural causes’.

“Living independently until the age of 110….. Despite visual and hearing loss, she maintained autonomy in the face of the dependence imposed by the regulations of a nursing home - refusing care and visitors she did not want, smoking in a public place, and insisting on her daily glass of port.”

Ritchie, 1997
Levels of organisation

- Atoms
- Molecules
- Cells
- Tissues (e.g. epithelium)
- Organ (e.g. stomach)
- Organ System (e.g. digestive system)
- Organism
THE CELLULAR BALANCE

Cellular damage & death

Cellular repair
Hallmarks of Ageing

Cell 153, June 6, 2013
1. Genomic Instability
In HGPS patients, the cell nucleus has dramatically aberrant morphology (bottom, right) rather than the uniform shape typically found in healthy individuals (top, right).
2. Telomere attrition
Replicative Senescence

- Cellular senescence – Hayflick Limit 52 (40-60)


- Mouse 14-28

- Tortoise 100
3. Epigenetic alterations. Alterations in the methylation of DNA or acetylation and methylation of histones, as well as of other chromatin-associated proteins, can induce epigenetic changes that contribute to the aging process.
4. Loss of Proteostasis
Oxidative stress (free radical) theory of ageing
5. Nutrient Sensing

Potentially conserved pro-ageing pathways
Available evidence strongly supports the idea that anabolic signalling accelerates ageing and decreased nutrient signalling extends longevity. Further, a pharmacological manipulation that mimics a state of limited nutrient availability, such as rapamycin, can extend longevity in mice.
Mitochondrial function has a profound impact on the aging process. Mitochondrial dysfunction can accelerate aging in mammals, but it is less clear whether improving mitochondrial function, for example through mitohormesis, can extend lifespan in mammals, though suggestive evidence in this sense already exists.
Key points

• High levels of pro-inflammatory markers in the blood and other tissues are often detected in older individuals and predict the risk of cardiovascular diseases, frailty, multimorbidity, and decline of physical and cognitive function.

• In individuals with obesity, visceral fat produces pro-inflammatory and chemotactic compounds and is infiltrated by macrophages, lymphocytes, and senescent cells with a senescence-associated secretory phenotype that contributes to inflammageing.

• Clinical trials suggest that modulating inflammation prevents cardiovascular diseases, but studies to explore the effects on other chronic diseases, frailty, and disability are scarce and controversial.
Ageing has to be understood in the context of evolution.
According to the ‘disposable soma theory’, organisms must compromise between energy allocation to growth and reproduction or somatic maintenance and repair.

Centenarian women’s reproductive systems age slowly.
Experiments on dietary restriction and genetic or chemical alteration of nutrient-sensing pathways

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<tr>
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<th>Life-span increase</th>
<th>Beneficial health effects</th>
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<tr>
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<td>Dietary restriction</td>
<td>Mutations/drugs</td>
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<tr>
<td>Yeast</td>
<td>3-fold</td>
<td>10-fold (with starvation/DR)</td>
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<td>Worms</td>
<td>2- to 3-fold</td>
<td>10-fold</td>
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<td>Flies</td>
<td>2-fold</td>
<td>60–70%</td>
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<td>Mice</td>
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<td>Monkeys</td>
<td>Trend noted</td>
<td>Not tested</td>
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<tr>
<td>Humans</td>
<td>Not determined</td>
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Fontana et al, 2010. Science
The brain as a potential regulator of organismal ageing
**Hormesis** (from Greek *hormæin*, meaning “to excite”) is the term for generally-favourable biological responses to low exposures to toxins and other stressors.

A non-monotonic curve
A very low dose of a chemical agent may trigger from an organism the opposite response to a very high dose

Repetitive mild stress exposure has anti-aging effects
- Exercise is a paradigm for hormesis in this respect
- Others are heat shock, irradiation, pro-oxidants, hypergravity and food restriction
- Some natural and synthetic molecules, such as celasterols from medicinal herbs and curcumin from a spice turmeric have also shown to have hormetric beneficial effects - "hormetins"
- Psychological Stress as a hormetin
Genetics

- Demographic selection
  - Evidence in medflies, nematode and humans
  - Apo E4 ↓ and E2 ↑ (Rebeck et al, 1994)
  - Apo B locus (Italian Centenarian Study)
  - HLA – DRw9 ↓ and DR1 ↑ (Okinawa Study)
  - Chr 4 D4S1654
  - Chr 11 11.p15.5
Parabiosis

Oxytocin
Blood borne chemokines – including CCL2/MCP-1 and CCL11/Eotaxin

Aging
- Decreased neurogenesis
- Impaired synaptic plasticity
- Impaired cognition

Rejuvenation
- Increased neurogenesis
- Unknown effect on synaptic plasticity?
- Unknown effect on cognition?

S.A. Villeda, T. Wyss-Coray / Autoimmunity Reviews 12 (2013) 674–677
Not only is she likely to live longer than he does, but she will help him live longer, too.

Why Do Women Live Longer?
Interventions that might extend human healthspan

- Clearance of senescent cells
- Stem-cell-based therapies
- Anti-inflammatory drugs
- Blood-borne rejuvenation factors
- Mitohormetics, mitophagy
- Dietary restriction; IIS and mTOR inhibition
- AMPK and sirtuin activation
- Elimination of damaged cells
- Activation of chaperones and proteolytic systems
- Epigenetic drugs
- Telomerase reactivation