LONGEVITY - how long can a human live??

Madame Jeanne Calment

On the 4th of August in 1997, the world doyen of longevity, Madame Jeanne Calment from Arles in the south of France, died aged 122 years, 5 months and 14 days.

• Why did she survive to such a ripe old age in excellent health and spirits while most perish long before?
• What eventually caused her demise when she was essentially in fine health?
Oldest Woman dies at 124

News report in 2002

The claimed oldest woman in the world, Maria Etelvina Dos Santos, has died in Brazil aged 124 years. She succumbed to a stroke at the weekend in the north-east provincial capital, Salvador.

A descendant of African slaves, Ms Dos Santos was born according to her official birth certificate on July 15, 1878. She leaves 5 grandchildren, 26 great-grandchildren, 39 great-great grandchildren and 4 great-great-great-grandchildren.

74 descendants

Ms Dos Santos had good health to the end. Her prescription for a long life “Always remain calm”
Many live to 111 to 114 yrs
Very rare beyond this age

“If I knew I was going to live this long, I would have taken better care of myself”
LONGEVITY (Life span) seems fixed but....... MORE PEOPLE are living longer

Improving the QUALITY OF LIFE of ageing people is now the major aim

Q: WHY do people AGE and die???

AND

Q: Can we extend the overall LIFESPAN ?? Immortality??
Quest for “Fountain of youth”, cloning
Maximum LIFE SPAN (longevity) varies between species

<table>
<thead>
<tr>
<th>Scientific name</th>
<th>Common name</th>
<th>Maximum lifespan (years)</th>
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<tbody>
<tr>
<td><strong>Primates</strong></td>
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<tr>
<td>Macaca mulatta</td>
<td>Rhesus monkey</td>
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<td>Pan troglodytes</td>
<td>Chimpanzee</td>
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<td>Gorilla gorilla</td>
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<td>Homo sapiens</td>
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<td><strong>Carnivores</strong></td>
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<td>Felis catus</td>
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<td>Ursus arctos</td>
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<td>Ovis aries</td>
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<td>Hystrix brachyura</td>
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<td><strong>Bats</strong></td>
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<td>Desmodus rotundus</td>
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<td>Pteropus giganteus</td>
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<td><strong>Birds</strong></td>
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<td>Streptopelia risoria</td>
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<td>Herring gull</td>
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<td>Aquila chrysaetos</td>
<td>Golden eagle</td>
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<td>Bubo bubo</td>
<td>Eagle owl</td>
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<td><strong>Amphibians</strong></td>
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<td>Xenopus laevis</td>
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<tr>
<td>Bufo bufo</td>
<td>Common toad</td>
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<tr>
<td>Cynops pyrrhogaster</td>
<td>Japanese newt</td>
<td>25</td>
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Reproduced with permission from Kirkwood (1985).
Maximum LIFE SPAN (longevity) varies between species

There is a great difference in the life-span of different mammals: small mice live for only about 2-3 years whereas elephants and humans normally live for about 60- 70 years. **WHY??**

From an evolutionary point of view the need to ensure that the individual lives to fulfil the biological function of reproduction is probably the crucial issue.
Age-related changes & decline of function in all systems and tissues

Some examples:

Eyes             vision changes
Skin             wrinkles, sagginess, cancers
Heart & cardiovascular narrowing of arteries, heart attacks
Joints           stiffness, inflammation
Bones            osteoporosis, fragility
CNS*             loss of memory, dementia
Muscles*         atrophy, weakness, loss of fast myofibres
Nerve cell survival in aging

We lose a lot of nerve cells with age. Here are a few survival statistics.

As we get older, specific structures within the brain suffer neural loss. Listed below are the percentage of cells remaining in a given area after age 50 (compared to the number of cells as a young adult). Note that some structures do not show any appreciable loss.

- **Occipital Cortex**: 50%
- **Locus Coeruleus**: 60%
- **Purkinje Cells**: 75%
- **Thalamus**: 100%

Contribution of denervation atrophy to sarcopenia?

1) CNS: motorneurone death, loss of NMJ, susceptibility of CNS to ROS.

2) Synapse (NMJ): do agents produced by myofibres maintain the NMJ, e.g IGF-1? Exercise and myokines e.g IL-6

3) Myofibre response to denervation: e.g Runx1
Age-related degeneration in all tissues

WHY????

Over 300 theories……this is from Holliday R (2006)

1. The best strategy for animals' survival is to develop to an adult, but not to invest resources in maintaining the body, or soma, indefinitely. In their natural environment, animals do not survive environmental hazards (predators, disease, starvation, and drought) to reach a long life span.

2. There is thus a trade-off between the investment of resources in reproduction, and the survival time of the soma.

3. This solves the problem of different rates of aging in different species, because those that develop and reproduce fast also have short life spans, and those that develop and reproduce slowly have long life spans.

4. Aging can be defined as the eventual failure of maintenance.

5. The major conclusion is that aging is multicausal.

6. The evolved design of many components of complex animals is incompatible with indefinite survival.

7. This in turn means that aging cannot be reversed, although it may be modulated
Age-related degeneration in all tissues
WHY???

Failure of maintenance

“We are all born as copies and die as originals”.

Reducing the number of errors would theoretically delay the ageing process and prolong life.
The aging of proteins in human cells

As the years go by, the quality and amount of proteins inside cells change. Here's what happens.

Some time ago, it was noticed that the older a cell became, the more protein accumulated in its cytoplasm. How much protein collected depended on the cell type. Cardiac muscle, skeletal muscle, liver and brain tissue all showed dramatic elevations. Since excessive levels can be hazardous to a cell's lifespan, finding out why the accumulation occurred became critically important.

Several biochemical mechanisms normally ensure a steady amount of proteins in younger cells. Described below is what happens when one of those fails.

**Brain:** amyloid and Alzheimers

**Eyes:** drusen and macular degeneration
When errors are NOT repaired leads to **dysfunctional proteins**: enzymes, structural, control of proliferation etc – **cancers**

*Xerodermal Pigmentosum* is a rare genetic disease where the DNA repair mechanisms are defective.

In the skin where the cells are exposed to UV light, mutations are caused and these cannot be repaired. This leads to many skin cancers which, if not all removed, lead to death by 25 years of age.
Cannot stop ageing.

Can slow it down and maintain good health to a greater age:

- Eat plenty of fruit and veges and a balanced diet,
- take regular exercise,
- be happy!

Cancer increases with age

**Fig. 6: Representative specific age incidence curves for human cancer: all cancers (male and female); cancer of stomach and duodenum (male); cancer of the breast (female). Figures from Australian experience (Lancaster).**
**FREE RADICAL FORMATION**

Free radicals are a form of toxic waste associated with the aging process. Here's what they are and how they form.

1. Free radicals are formed in the cell's mitochondria. This bean-shaped organelle, split crossways in the illustration to the left, functions like a tiny battery. ATP is the chemical that stores the energy.

2. This power generation, like most manufacturing processes, produces toxic waste. The waste is in the form of excess electrons.

3. The reason we breathe air is to get rid of this toxic waste. Oxygen, like a sponge, normally soak up excess electrons.

**WHEN IT BREAKS DOWN...**

The oxygen absorbs the offending electrons in the following way: it reacts with excess hydrogen in the cell. The combination of oxygen, hydrogen and electrons form a water molecule. This water is subsequently excreted or used for other purposes.

Sometimes this process breaks down and the electron binds to other molecules in the cell. Such chemicals possessing unpaired electrons are called free radicals. Free radicals are highly reactive and cause a lot of internal cellular damage. Oxygenated free radicals are also called ROS (Reactive Oxygen Species) molecules.

**ROS = Reactive Oxygen Species**

**RADICAL DAMAGE**

ROS (reactive oxygen species) molecules can do a lot of damage to the interior of cells – and cells have evolved mechanisms to fight them. Here's an outline of the battle.

**FIGURE 41**

**FIGURE 42**

Cells have evolved molecular weapons to fight the effects of ROS. These armaments come in many types, from simple organic molecules to complex vitamins. Regardless of their structure, these biochemicals are termed anti-oxidants.

**ANTI-OXIDANTS**
- Uric acid
- Glutathione
- Ascorbic acid
- Vitamin E

**PROTEINS**
- Catalase
- Heme oxygenase
- Superoxide dismutase

The free-radical theory of aging hypothesizes a reduction in anti-oxidant levels. The molecules that govern their synthesis and regulation break down in later adulthood. This allows a toxic build-up of ROS molecules and increased damage to cells.
Replicative Senescence and the Hayflick number

The idea that all normal diploid vertebrate cells have a limited capacity to proliferate is known as the Hayflick limit or replicative senescence.

From studies of human fibroblasts in tissue culture, it is concluded that after about 50-80 doublings they become non-dividing, although they remain viable.
Replicative Senescence *Hayflick number* and Immortalisation (cancer)

**FIGURE 1.** Schematic representation of viable terminal proliferation arrest (TPA) states in human fibroblasts. Normal cells permanently cease dividing in a state referred to as senescence. Other TPA states act as barriers to continued proliferation following various genetic or epigenetic changes. The genetic changes responsible for immortalization are essentially unknown, but they are associated with the activation of a telomere maintenance process such as telomerase.
The tips of human chromosomes may be

**The molecular clock of aging**

Telomeres, the very ends of chromosomes may count-down the life-span of a human cell. Here’s what telomeres are and how they function in human aging.

A telomere is the region on the very tip of chromosomes. They are composed of a repeating series of six nucleotides, TTAGGG. A typical human telomere may have more than 1500 such repeats in it. Their relevance to the aging process is described on the next page.

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**TELOMERE SHORTENING**

Telomerase & cell replication

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1. When a cell undergoes replication, most of the chromosome is duplicated.

2. The duplicating machinery is constructed in such a way that part of the tip is not replicated.

3. During division, one of the two new cells gets a shortened segment.

4. As progressive cell divisions occur, the overall chromosomal length gets shorter and shorter. A cell’s age can be determined by examining telomere length.

There are studies which suggest this successive loss is involved in aging. When the chromosomes reach a certain length, a self-destruct mechanism is triggered within the cell. This successive loss of telomeres acts like a ‘death clock’ and strengthens the relationship between aging and programmed cell death.
Replicative Senescence and the
_Hayflick number_

Does this apply _in vivo_??

Rubin (2002)
… questions the relevance of the _in vitro_ observations to the situation _in vivo_. For example, cells of the epithelium of the intestine and also the epidermis undergo 1,000s of divisions in a lifetime without a sign of senescence!

…. proposes that
“_The concept of a genetically predetermined number of human fibroblast replications, and its implied extension to other cells, is based on an ARTIFACT resulting from the damage accumulated by the explanted cells during their replication in the radically foreign environment of cell culture_”.

Factors that influence life span

- **Genetics**  centenarians: age-related diseases  
  e.g Xerodermal Pigmentosum

- **Accidents**  events during intrauterine development, illnesses and disease throughout life, apart from physical and mental trauma

- **Behaviour**
**Behaviour/life style**

****Note: these items are of crucial importance and all can be regulated****

(1) Diet
Endless fads: multivitamins, minerals, anti-oxidants (Vit C, red wine), melatonin etc.
“fountain of eternal youth”.

Human trials and experiments difficult to justify and verify. e.g. what age start the intervention?

Animal Experiments take a long time – therefore often test in animals with short life spans – flies, worms…
Many mutations in flies, worms, mice extend life span
Decreasing IGF-1 increases life span

Main thing that extends life of animals is ‘dietary restriction’.
Behaviour/life style

****Note: these items are of crucial importance and all can be regulated****

(1) Diet

(2) Exercise
Regular exercise affects mind/stress/depression, plus body e.g cardiovascular system, skeletal muscle strength, general oxygenation, strengthens bones/reduces osteoporosis.
Even modest weight lifting by frail old people in homes gives feeling of ‘well being’ and health/happiness.

(3) Attitude
The attitude/zest for life of Jeanne Calment contributed to her longevity. Mental attitudes affect the immune system…Stress, “mind over matter”. Yoga/meditation…….
Having a pet keeps older people far ‘happier’.
Cannot stop ageing.

Can slow it down and maintain good health to a greater age:
bottom line is

*Eat plenty of fruit and veges and a balanced diet,*
*take regular exercise,*
*be happy!*