Why and How Are Living Longer?

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Jeanne Calment – longest recorded human lifespan (122y 5m)
Why and How Are We Living Longer?

• Why has the continuing increase in longevity taken the world by surprise?
• Do we understand what is driving it?
• What are the consequences for health in old age?
• Can we extend health span further?
• What will be necessary to make this possible?
• What are the barriers to further progress?
Humanity’s Greatest Success Story?
Border Crossing – Burkina Faso to Ghana 1990

- Young Today Old Tomorrow
- Help Care for the Aged
- Oral Rehydration Salts (ORS)
- Dehydration from diarrhoea can cause death. To stop dehydration, use ORS.
The Continuing Increase in Life Expectancy

Declining early/mid-life mortality  Declining later-life mortality
Early or Late – Which Matters Mosts?

• Developmental origins of health and disease
  Barker et al *Lancet* 1989

• Late life changes in health experience
  – Following German re-unification, East Germans gained near parity in life expectancy within two decades
    Max Planck Institute for Demographic Research 2011
  – In Japan, data from the 1900, 1910 and 1920 birth cohorts show nearly identical exposure to early life mortality (prior to 1945) but progressively increasing life expectancy based on post-1945 improvements.
    Engelaer et al *Ann Rev Gerontol Geriatrics* 2013
Why and How Are We Living Longer?

• Why does ageing occur, and what can this tell us about its intrinsic mechanistic basis?
• What roles are played by environmental and lifestyle factors?
• What biological, medical and psychosocial factors influence health trajectories in later life?
Why There is No Genetic Programming FOR Ageing

- Animals in nature mostly die young.

- There is neither need nor opportunity to evolve a programme.

- Programmed ageing, if it existed, would be ‘unstable’.

- No immortal mutants are observed.

Kirkwood & Melov *Current Biology* 2011
Evolution and Ageing

The "Disposable Soma"
Kirkwood *Nature* 1977
Why Ageing Occurs

- The body is programmed for survival. However, there was no evolutionary pressure to invest in a body that might live forever.

- Ageing is caused by the accumulation of damage.

- Longevity is regulated by efficiency of somatic maintenance.

Disposable Soma
Kirkwood Nature 1977
Genetic control of longevity

- Environmental modulation

- Period of longevity assured by maintenance and repair

- Antioxidant defences
- DNA repair
- Protein turnover
Correlation Between Cellular Stress Resistance and Mammalian Species Life Span

Kapahi, Boulton, Kirkwood  Free Rad Biol Med 1999
Twin Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Coefficient of heritability</th>
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<tbody>
<tr>
<td>McGue et al (1993)</td>
<td>0.22</td>
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<tr>
<td>Herskind et al (1996)</td>
<td>0.25</td>
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<tr>
<td>Ljungquist et al (1998)</td>
<td>&lt;0.33</td>
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</tbody>
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Genes account for about 25% of what determines human longevity.

The relevant genes are numerous, mostly of small individual effect, and they influence somatic maintenance and metabolism.

Schachter, Cohen, Kirkwood *Hum Genet* 1993
Kirkwood, Cordell, Finch *Trends Genet* 2011
Beekman et al *Aging Cell* 2013
Deelen et al *Hum Mol Genet* 2014
The Deep Mechanisms of Ageing

DNA

RNA

PROTEIN

Copying errors, Telomere shortening
Mutations e.g. ROS
Transcription errors
Translation errors
Damage, denaturing e.g. ROS

Antioxidants

Chaperones

Degradation or aggregation (e.g. β-amyloid)

ROS, etc

ROS, etc

ATP

mtDNA

ROS, etc

ATP
Each cell division is accompanied by inevitable somatic mutation. Damage Accumulates From Day One. 

Age-Related Increase in Frequency of $Hprt$ Mutations in Mice

Odagiri et al Nat Genet 1998
Abnormal Protein Aggregation in Ageing Brain
Telomeres – Division Counter, Tumour Defense (or something more?)

- Telomeres protect chromosome ends – they shorten with cell division (end-replication problem); and this is accelerated by biochemical stress.
- Critically short telomeres cause growth arrest.
- Prematurely short telomeres are linked with increased risk of age-related disease and diminished survival.

Telomerase
- Protects against end-replication problem.
- Inactive in most somatic cells.
- Active in germ-line, stem cells and most cancers.
Mitochondrial Mutations Accumulate with Ageing

Ciliary epithelium (eye)

Similar age profiles across species

Status Report on an Aged Human Cell

- DNA damage foci
- Telomeres
- Overlap of damage foci with telomeres
- Mitochondria with high membrane potential
- Mitochondria with low membrane potential
Apoptosis is a mechanism for deleting unwanted cells.

Cells may be unwanted during development (tissue shaping), haematopoiesis (auto-reactive immune cells), or because they become damaged with increased risk of adverse consequences, e.g. malignancy.

Frequency of apoptosis increases with age, because age is associated with damage.
- E.g. stem cells in old (30m) mice twice as sensitive to very low dose genotoxic stress (1Gy gamma-irradiation) as in young mice (6m).

Enhancing the pro-apoptotic pathways in transgenic mice confers increase protection against cancer but accelerates ageing through more rapid loss of tissue cellularity.
Ageing of Human Fibroblasts *in vitro*

replicative senescence

1 month
PD 10

3 months
PD 25

6 months
PD 50

PD: population doublings – measure of cell multiplication
Senescence is a regulated response to damage mediated by a positive feedback loop between DNA damage and mitochondrial ROS generation. Passos et al. *Mol Sys Biol* 2010.

Cellular senescence is causally implicated in generating age-related phenotypes and removal of senescent cells can prevent or delay tissue dysfunction. Baker et al *Nature* 2011.

Senescent cells produce and secrete various bioactive molecules and can induce a “bystander effect” within surrounding tissue. Nelson et al *Aging Cell* 2012.
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Ageing Process and Its Malleability

Age-related Frailty, Disability, and Disease

Accumulation of Cellular Defects

Random Molecular Damage

- INFLAMMATION
- ANTI-INFLAMM.
- GOOD LIFESTYLE
- GOOD NUTRITION
- STRESS
- ENVIRONMENT
- BAD NUTRITION

Kirkwood *Cell* 2005
76,707 men and women aged 60+
No CHD, stroke or cancer at enrolment
Median follow up 89 months (4047 deaths)
Adherence to Mediterranean diet assessed on 10-point scale:
0 (poor)...9 (high)

2 unit increment in ‘Mediterranean-ness’ of diet results in 8% reduction of overall mortality

Trichopoulou A et al. (2005) BMJ 330, 991-997
The Benefits of a Healthy Lifestyle

Exercise significantly improves health across the life course and delays diseases linked with ageing.

“I never thought turning eighty would be so much fun!”
All Cause Mortality per 10,000 person years

P = 0.001

P = 0.005

Upper 3\textsuperscript{rd}

Middle 3\textsuperscript{rd}

Lower 3\textsuperscript{rd}

Tertiles of muscular strength

Cancer Mortality per 10,000 person years

P = 0.02

P = 0.007

8762 men

A few minutes on the Newcastle metro can take years off your life ...

Socioeconomic Gradient

Age of expected onset of limiting long-term condition for 55yr old person

Courtesy Prof Peter Gore/Prof Carol Jagger/ONS
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Factors Influencing Health Trajectories in Old Age

- Genes
- Nutrition
- Lifestyle
- Environment
- Socioeconomic status
- Attitude

These factors and their interactions are being studied in the Newcastle 85+ Study; a 7-year prospective study in more than 1000 individuals born in 1921.
No one has perfect medical health at age 85.
Yet, 78% rated their health compared with others of the same age as “good” (34%), “very good” (32%) or “excellent” (12%).

Collerton et al *British Medical Journal* 2009
A quarter of men and a sixth of women have no important functional limitation at age 85.

Jagger et al *BMC Geriatrics* 2011
Newcastle 85+ Study – topics reported to date

- Cognitive assessment
- Nutritional intake
- Multi-morbidity
- Frailty
- Biomarkers
- Genetics
- Mitochondrial haplotypes
- Capability and care needs
- Arthritis and joint pain
- Falls
- Visual impairment
- Inflammation and immunosenescence
- Heart disease
- Sleep and activity
- Male-female disability paradox
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Barriers to Changing the Status Quo

- Distaste – “I’d rather not think about it”
- Ignorance – “I’m just not that interested (yet)”
- Fatalism – “I can’t change it anyway”.
- Negative stereotyping – “Old people are losers”.
- Youth bias – “We must invest in the future!”
- Tunnel vision – “This is how it has to be”
- Failure to engage – “I know all about ageing and it’s just …”
- Short-term’ism – “I’ll deal with it when I’ve fixed the immediate crisis”.
Thank you

National Institute for Health Research