"Silent Transformations"
Nanyang Technological University
7-9 March 2016

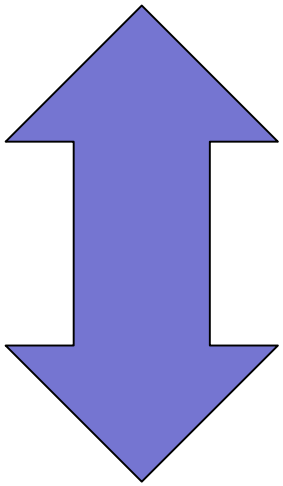
Dynamics of ageing: a silent transformation caused by "noise"

Tom Kirkwood

Newcastle University Institute for Ageing, and University of Copenhagen Centre for Healthy Ageing

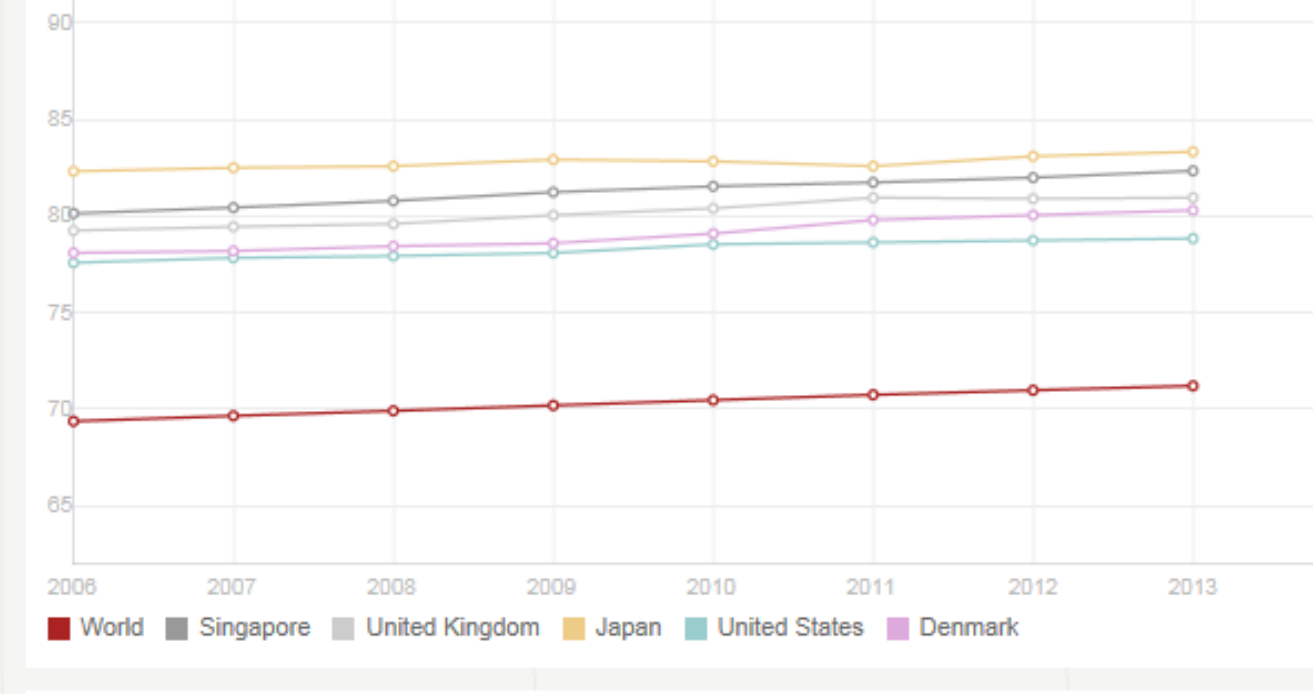
The Silent Transformations of Ageing

Silent transformation of the body



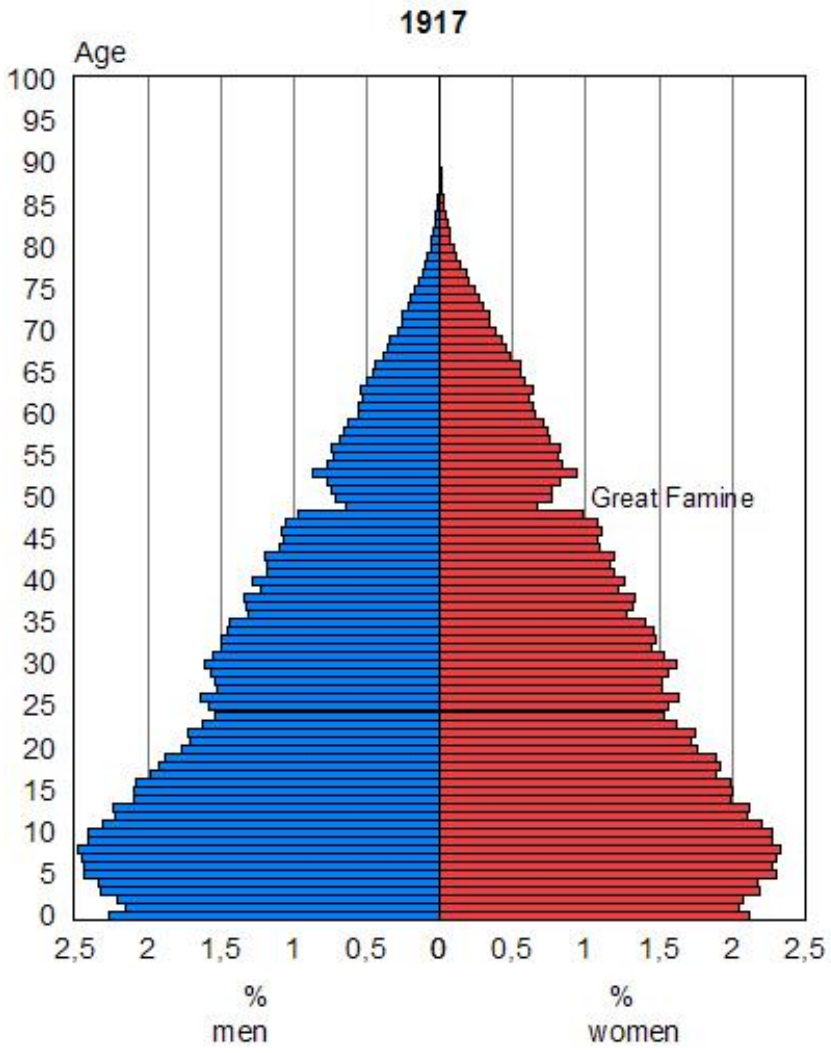
Silent transformation of society

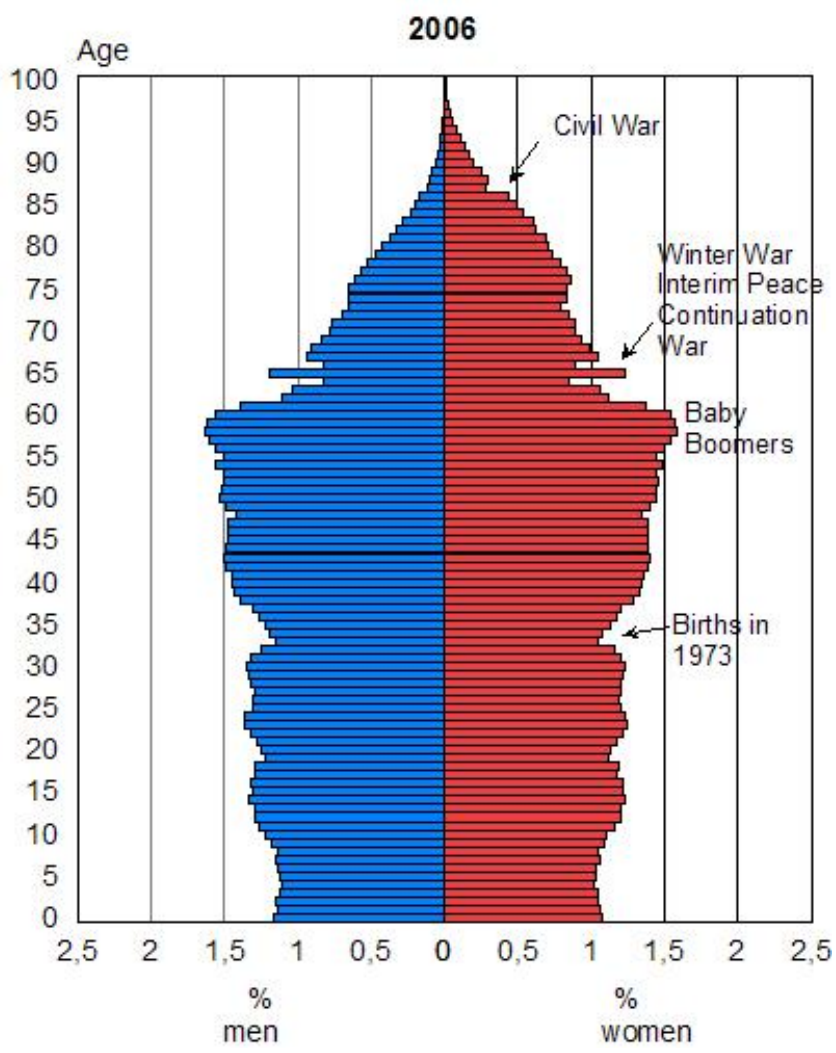
Recent trends in life expectancy (2006-2013)



Source: http://data.worldbank.org

Transformation of Population Structures



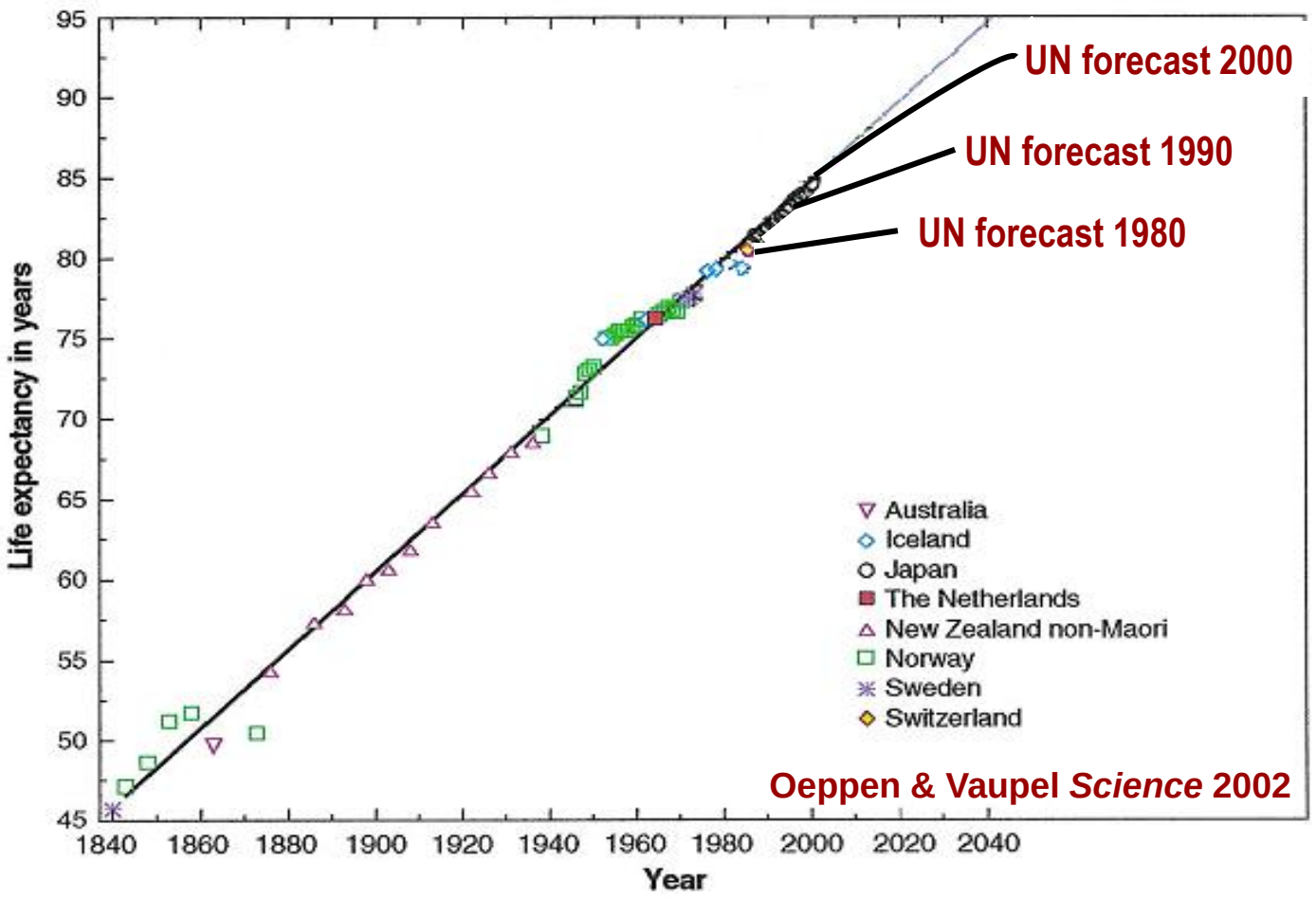


Source: Statistics Finland www.stat.fi

Transformation even in the poorest regions

Photo: Immigration hut at border between Burkina Faso and Ghana

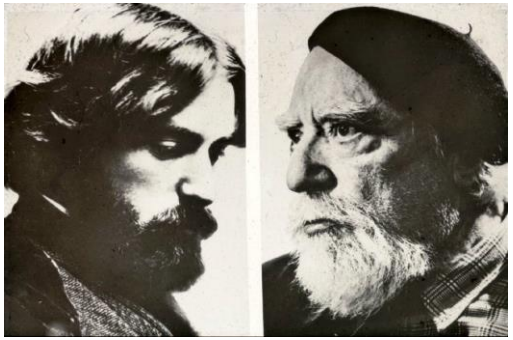
Unexpected Continuation of Growth in Life Expectancy



Declining early/mid-life mortality

Declining later-life mortality

Understanding the silent transformations of ageing



- Why and how does ageing occur?
- What is the relationship between ageing and disease?
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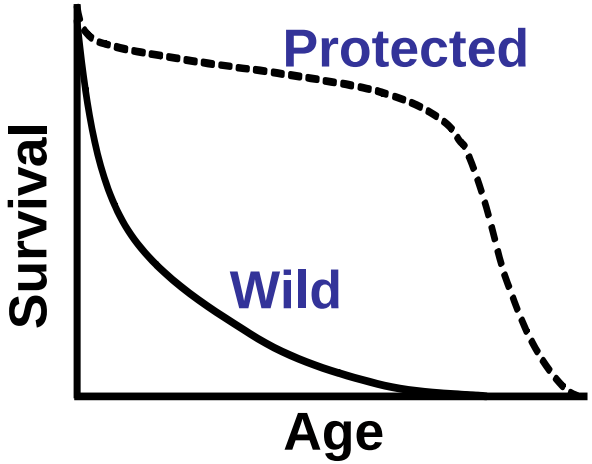
- What accounts for the individuality of ageing?
- Changing the mind-set

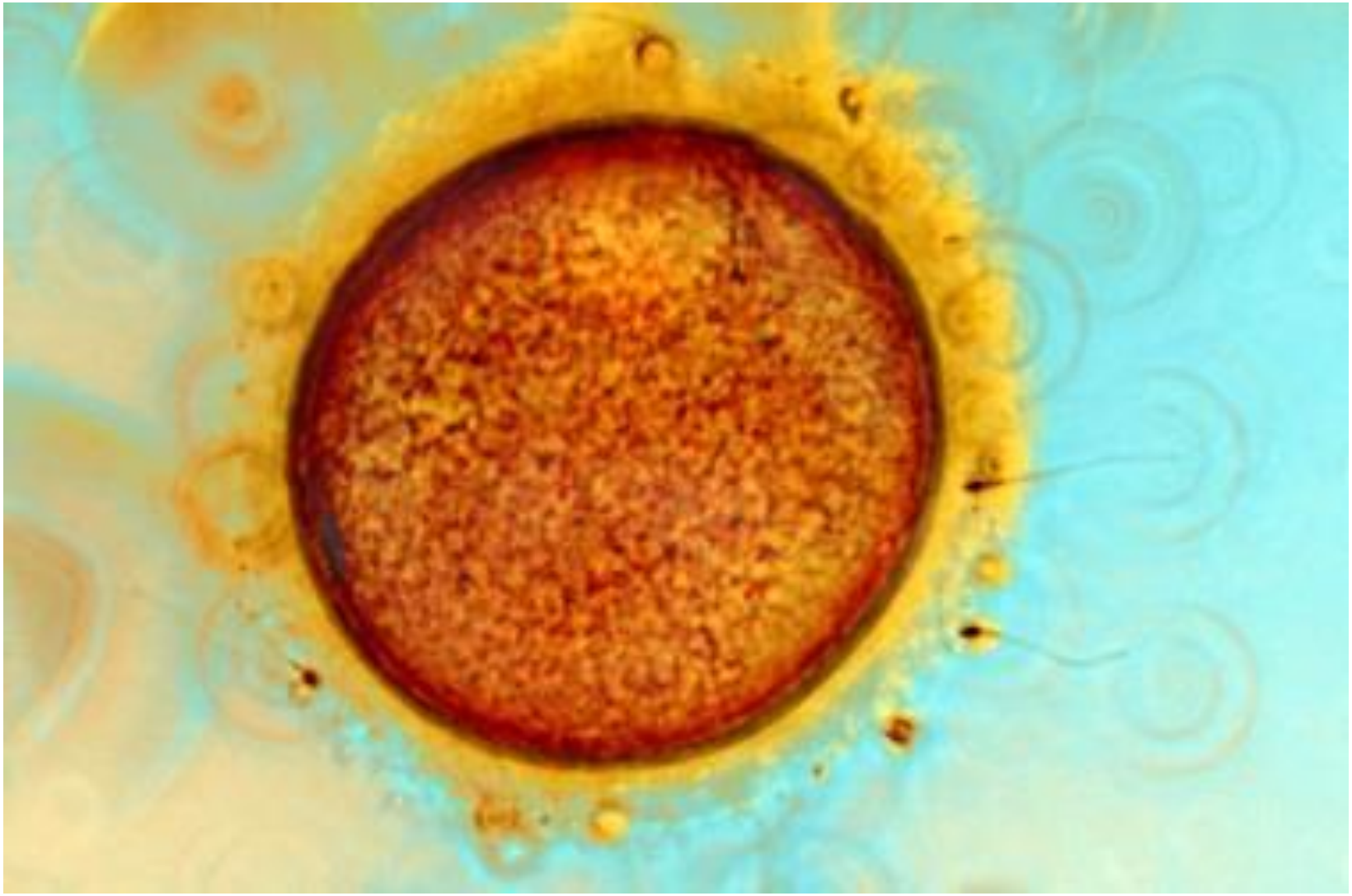
Why There is No Genetic Programming FOR Ageing

- Animals in nature mostly die young.
- There is neither need nor opportunity to evolve a program.
- Programmed ageing, if it existed, would be ‘unstable’.

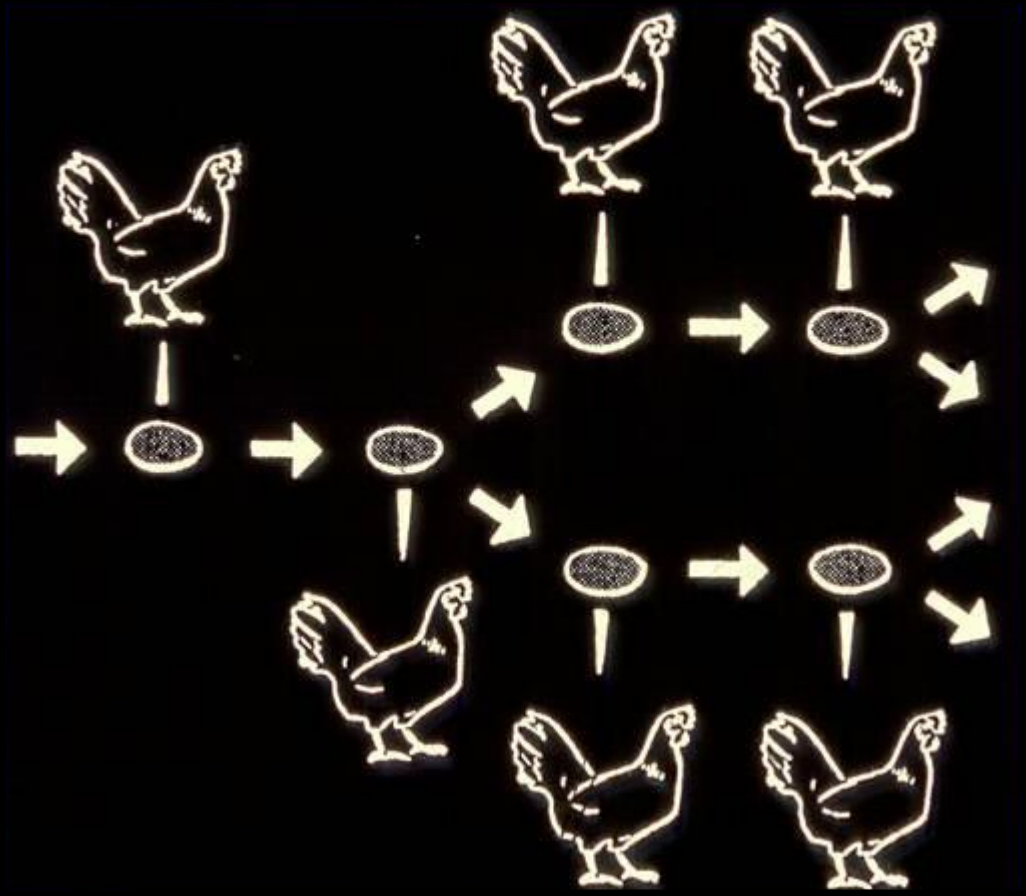


Kirkwood & Melov *Current Biology* 2011

Life – a Sexually Transmitted Condition with an Invariably Fatal Outcome

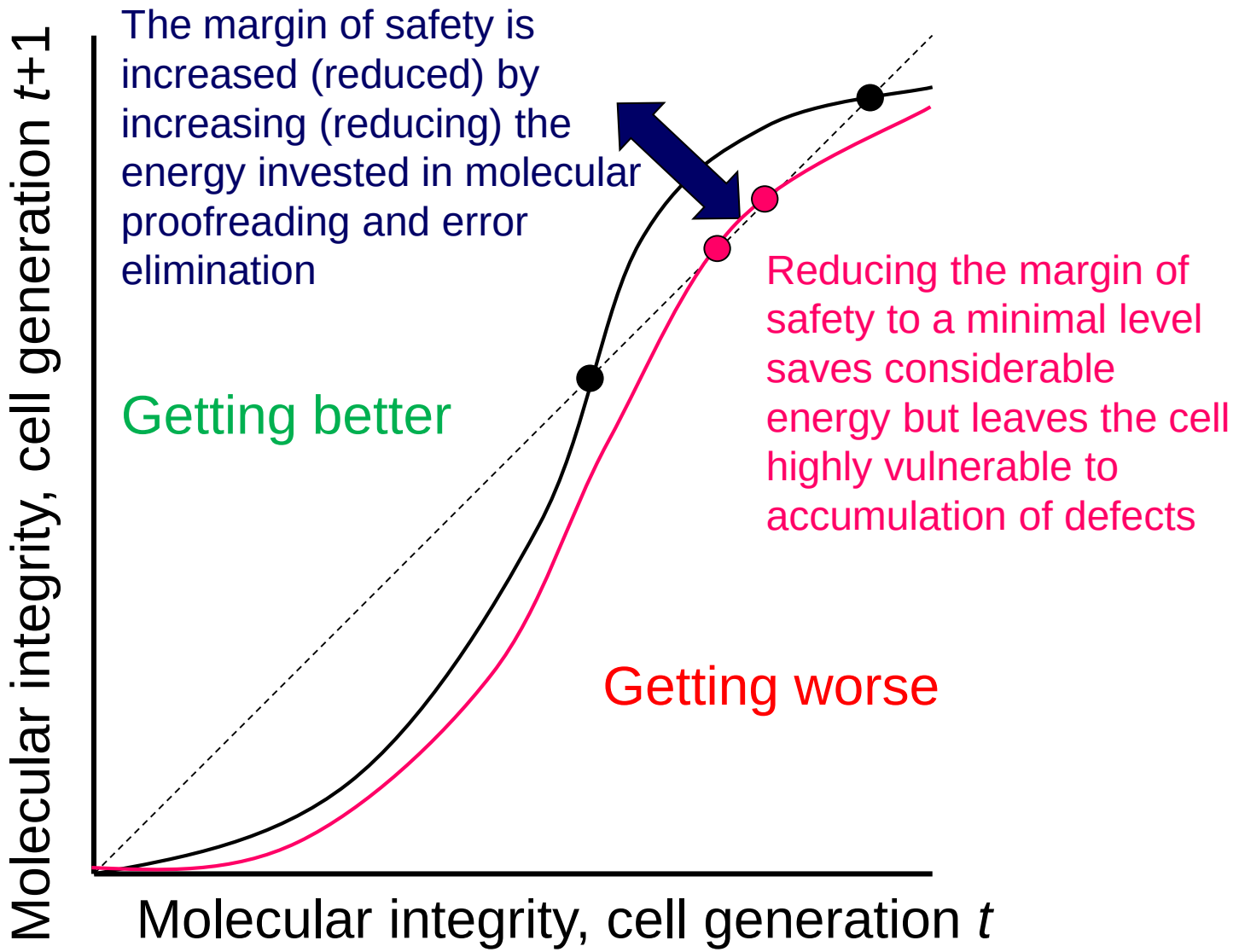


Immortal Germ-Line – Mortal Soma



August Weismann

Cellular Stability and Instability

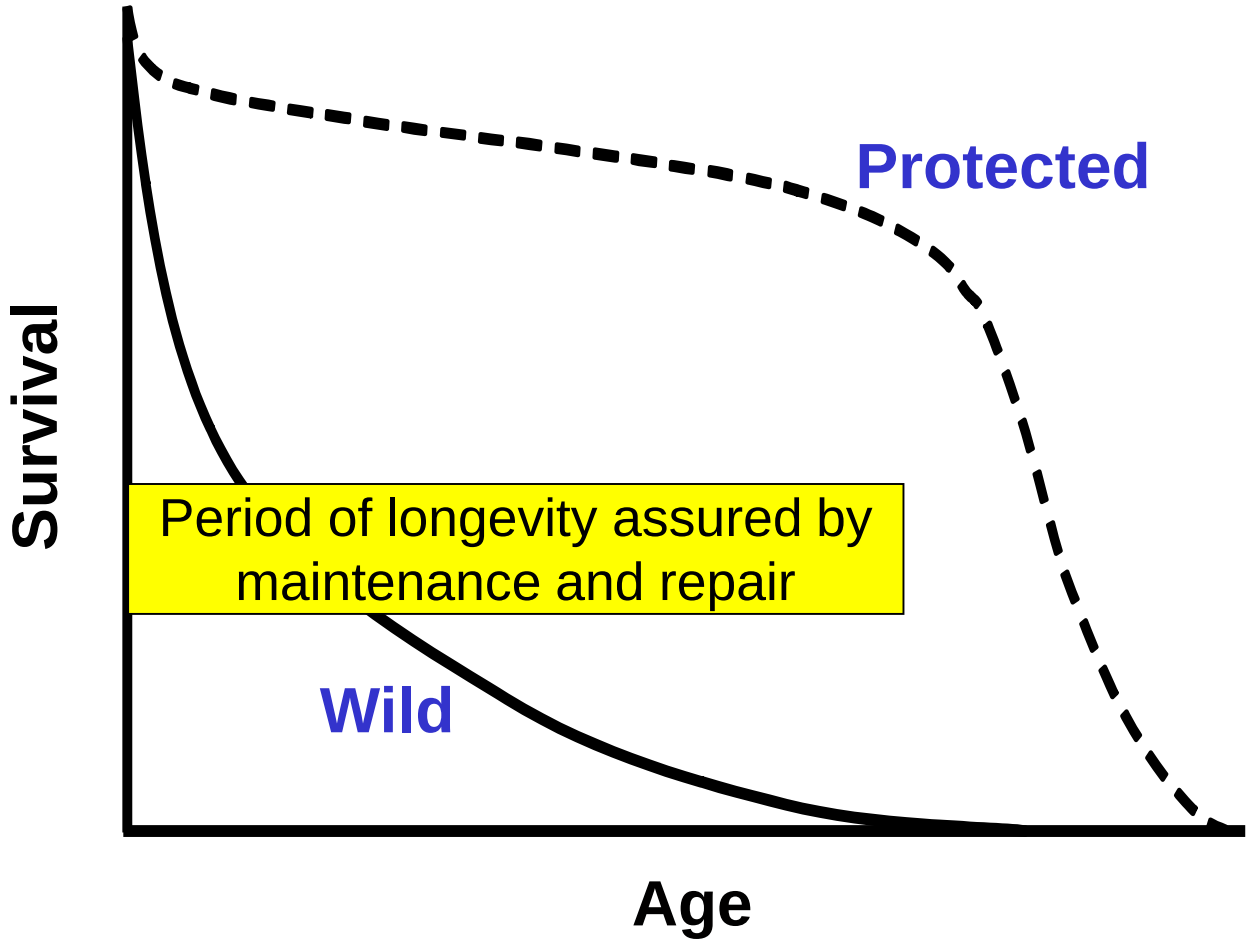


Kirkwood & Holliday *J Mol Biol* 1975

THE CENTRAL PROBLEM OF ALLOCATING METABOLIC RESOURCES

Kirkwood (1981) in *Physiological Ecology: An Evolutionary Approach to Resource Use* (eds Townsend & Calow)

DISPOSABLE SOMA THEORY



Kirkwood *Nature* 1977

Mechanistic Implications of Disposable Soma Theory

- Maintenance & repair high in germ-line; reduced in soma
- Ageing caused primarily by damage
- Longevity regulated by resistance/repair

- Inherently stochastic
- Multiple mechanisms; Complexity
- Plasticity and trade-offs

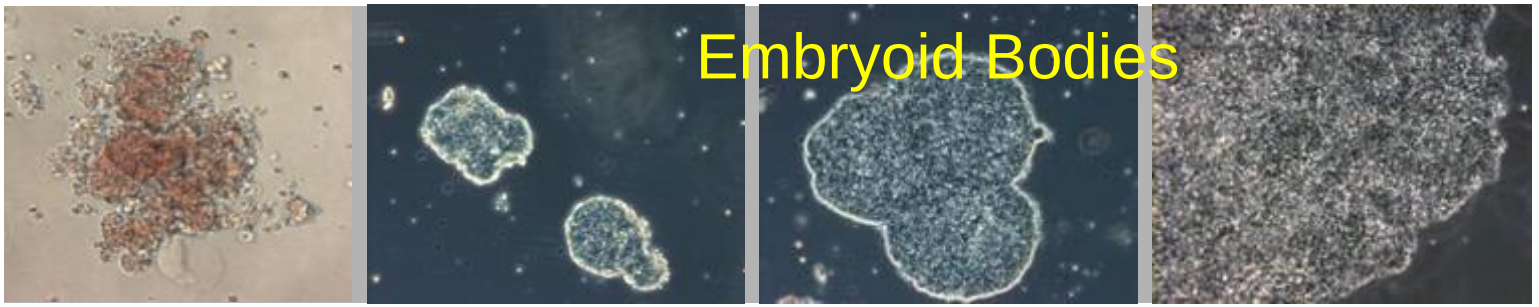
Immortality of the Germ-line vs Disposability of the Soma

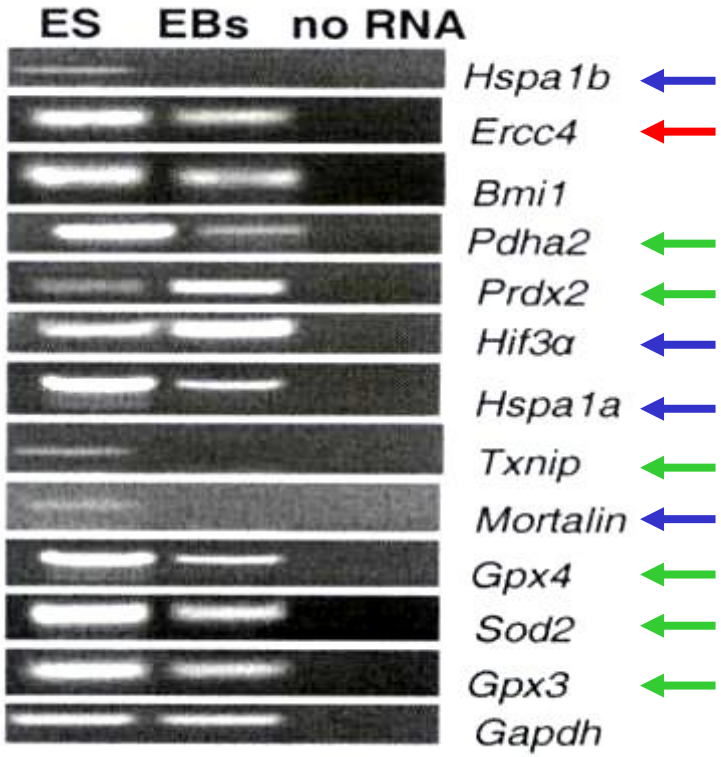
"Accuracy in the germ line is vital but a high level of accuracy in somatic cells may be a luxury our genes do better to forego.

Ageing may, therefore, be the result of … switching off the mechanisms responsible for high accuracy at or around the time of differentiation of somatic cells from the germ line."

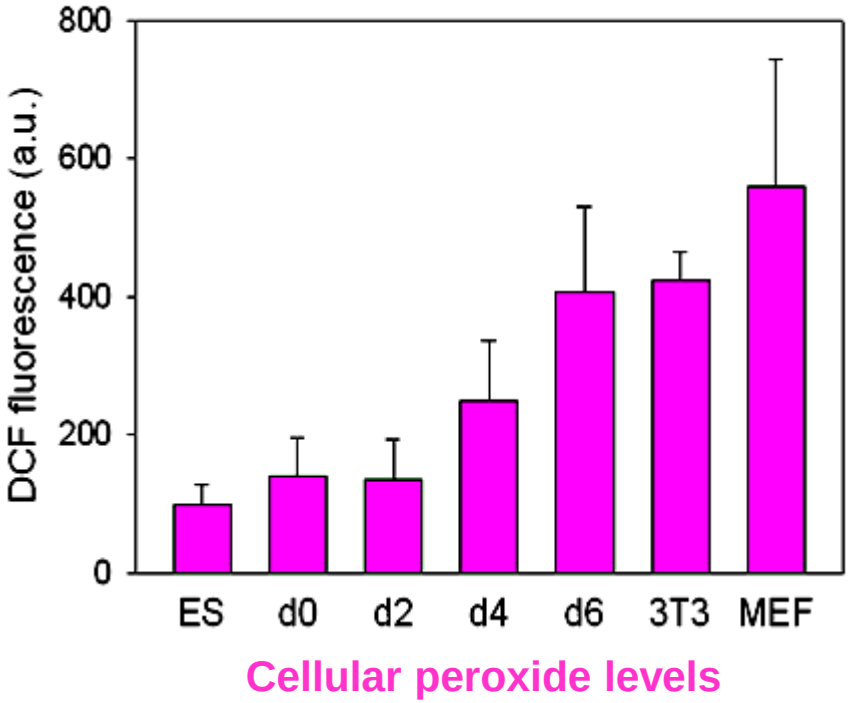
Kirkwood *Nature* 1977

Germ Cells are Special – Embryonic Stem Cells Lose this Status as they Undergo Differentiation





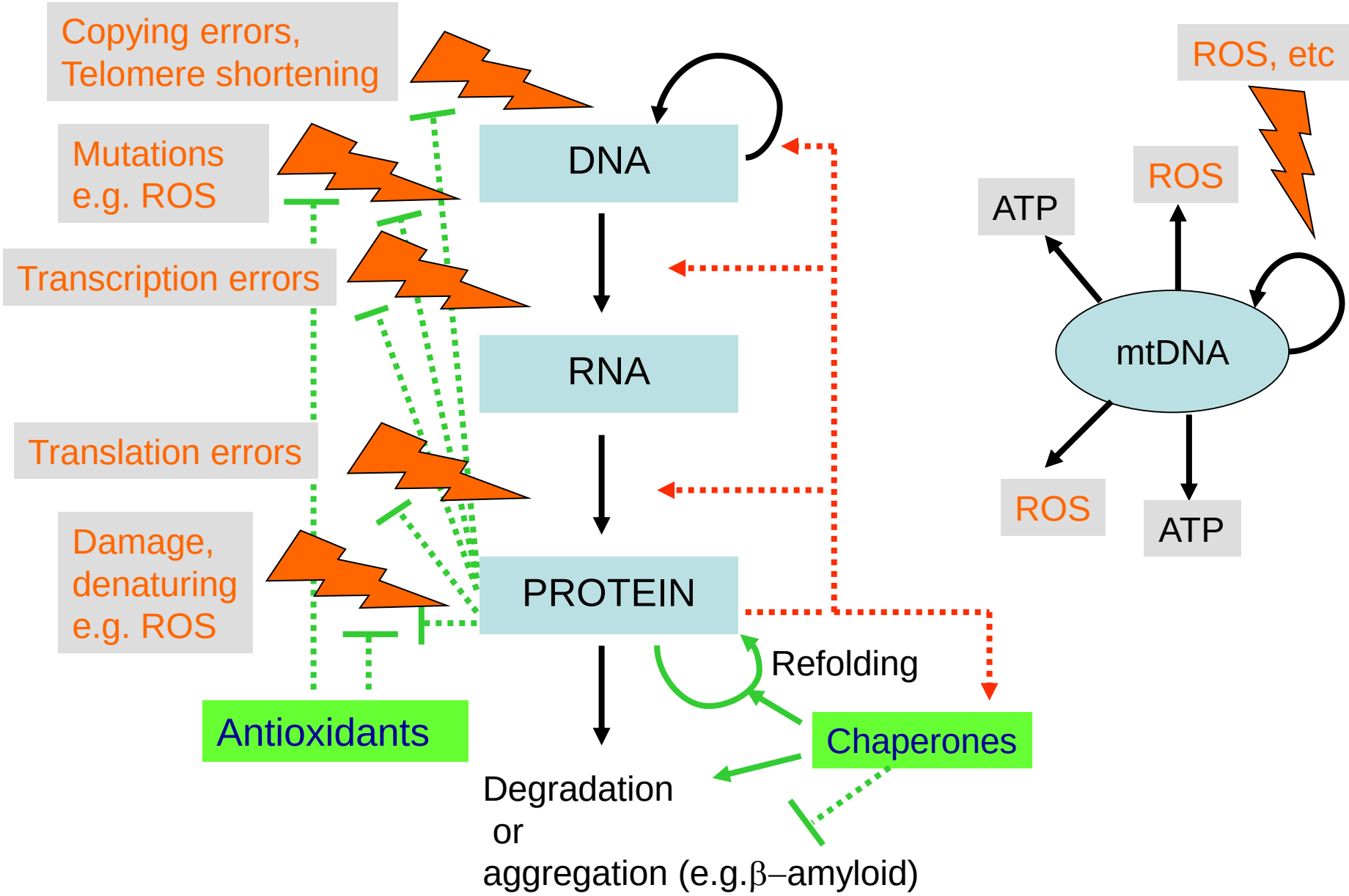
AO defence, DNA repair, chaperones



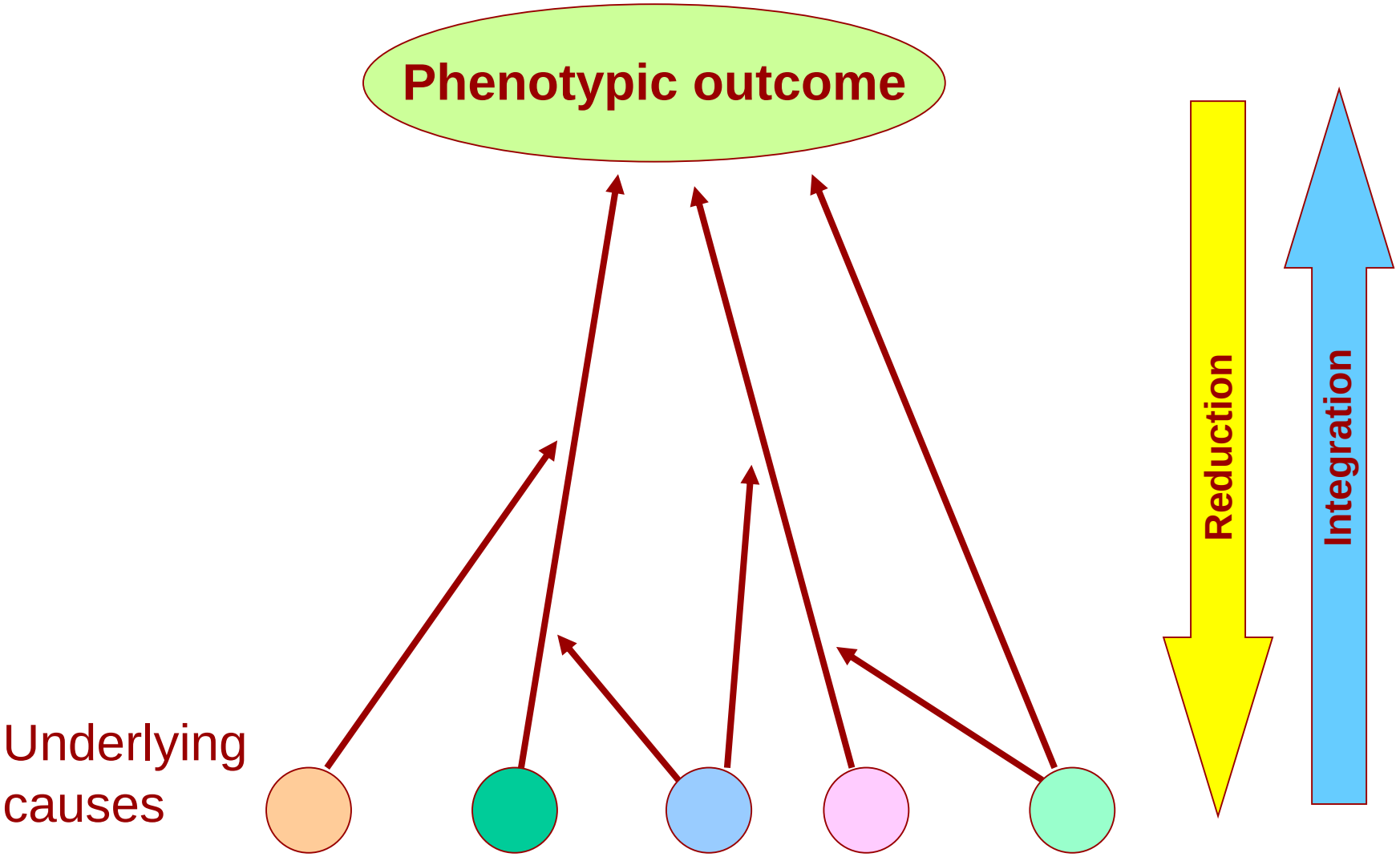
Cellular peroxide levels

Saretzki et al. *Stem Cells* 2004, 2008

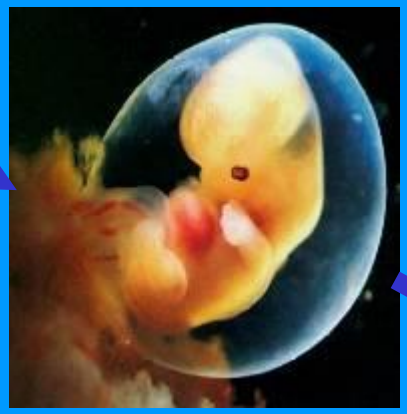
‘Noise’ Drives the Ageing Process



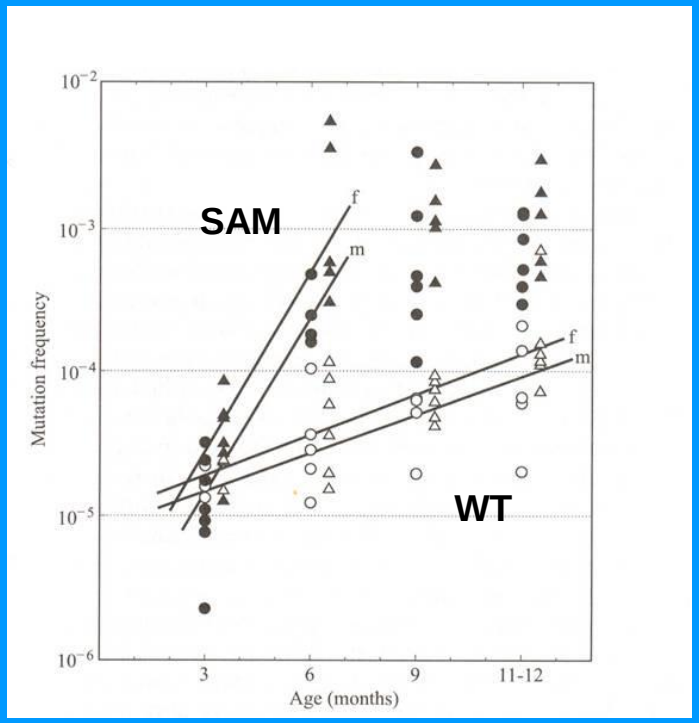
The Importance of a Systems Approach



Damage Accumulates From Day One

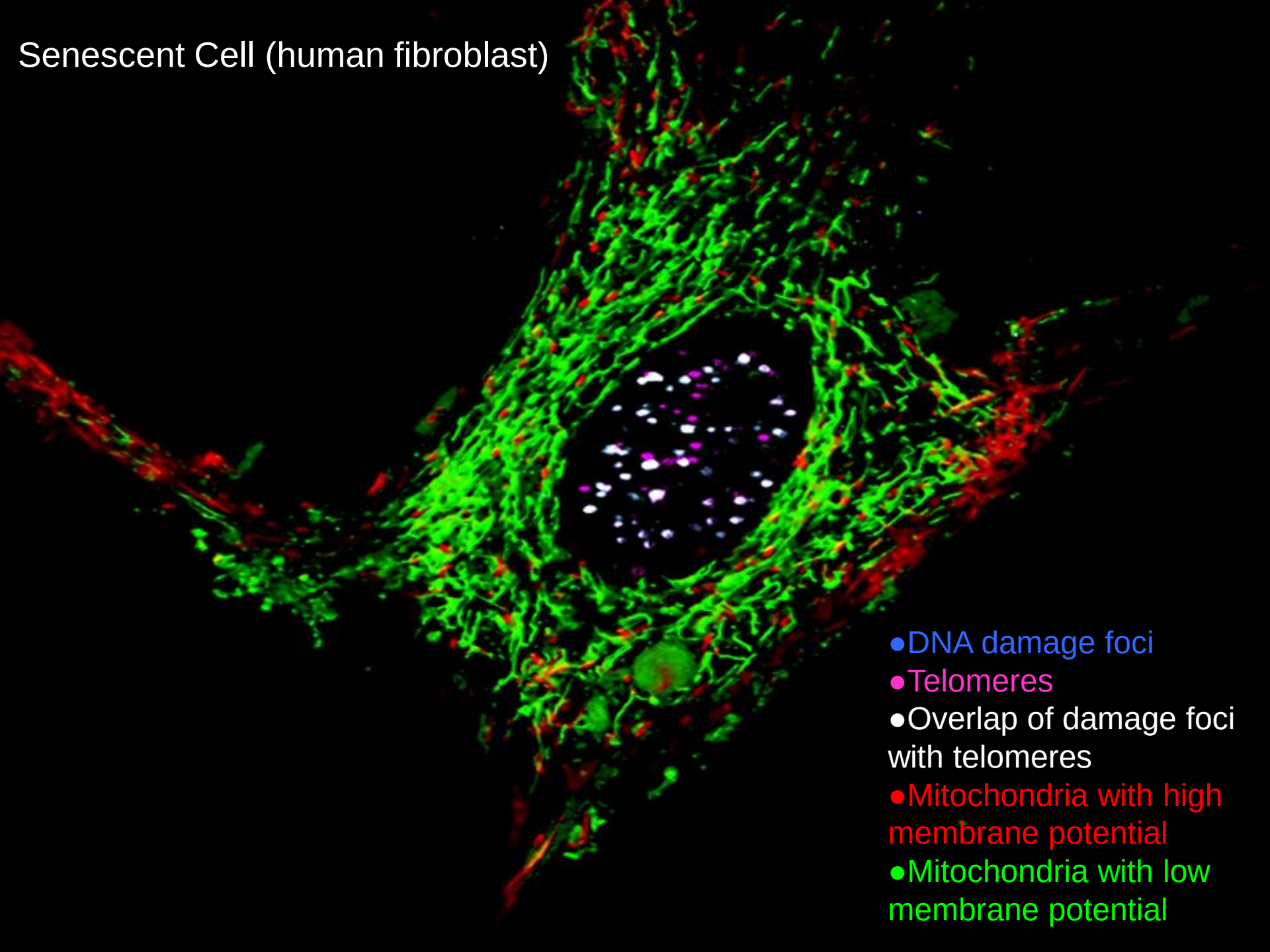


Each cell division is accompanied by inevitable somatic mutation



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

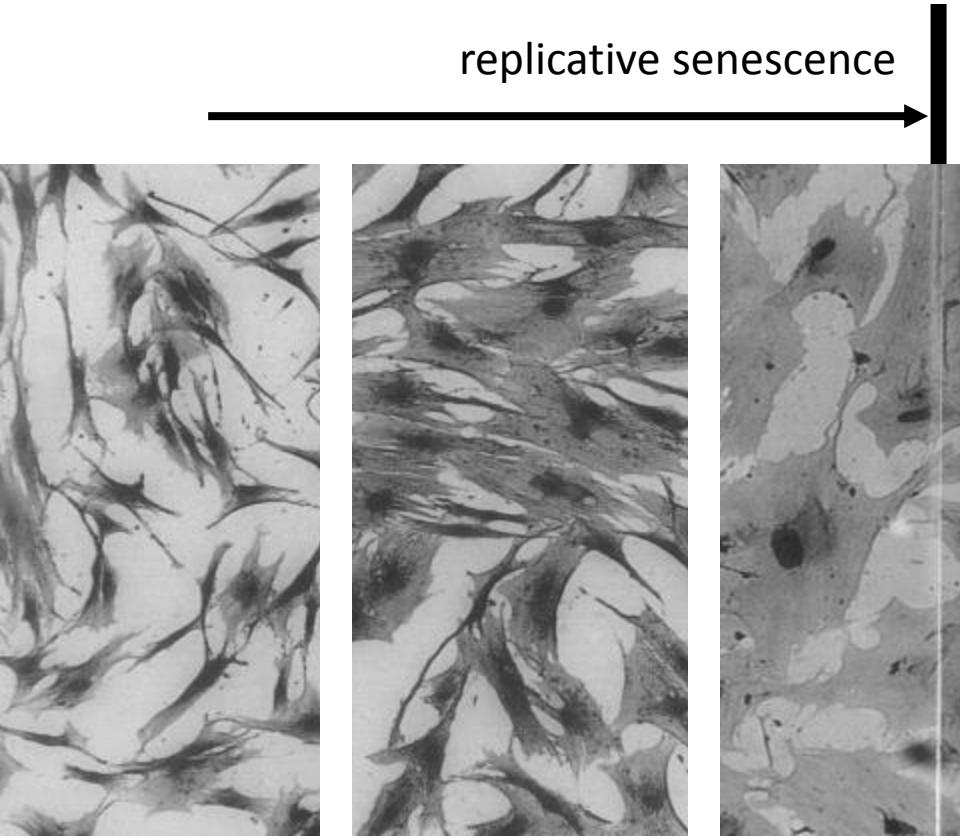
Odagiri et al *Nat Genet* 1998


Senescent Cell (human fibroblast)
●DNA damage foci
●Telomeres
●Overlap of damage foci with telomeres
●Mitochondria with high membrane potential
●Mitochondria with low membrane potential

Cellular Responses to Damage – Apoptosis

- Apoptosis acts to delete 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.
- Enhancing pro-apoptotic pathways in transgenic mice confers increased protection against cancer but accelerates aging through more rapid loss of tissue cellularity.

Ageing of Human Fibroblasts *in vitro*: The Hayflick "limit"



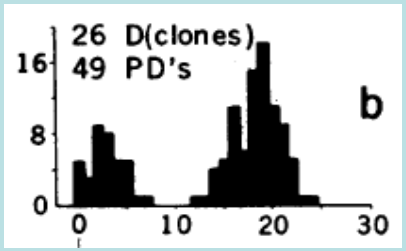
1 month
PD 10

3 months
PD 25

6 months
PD 50

PD: population doublings – measure of cell multiplication

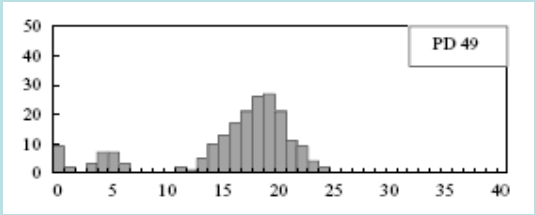
Systems Modelling ⟺ Experiment



Smith & Whitney 1980

Data

Theory

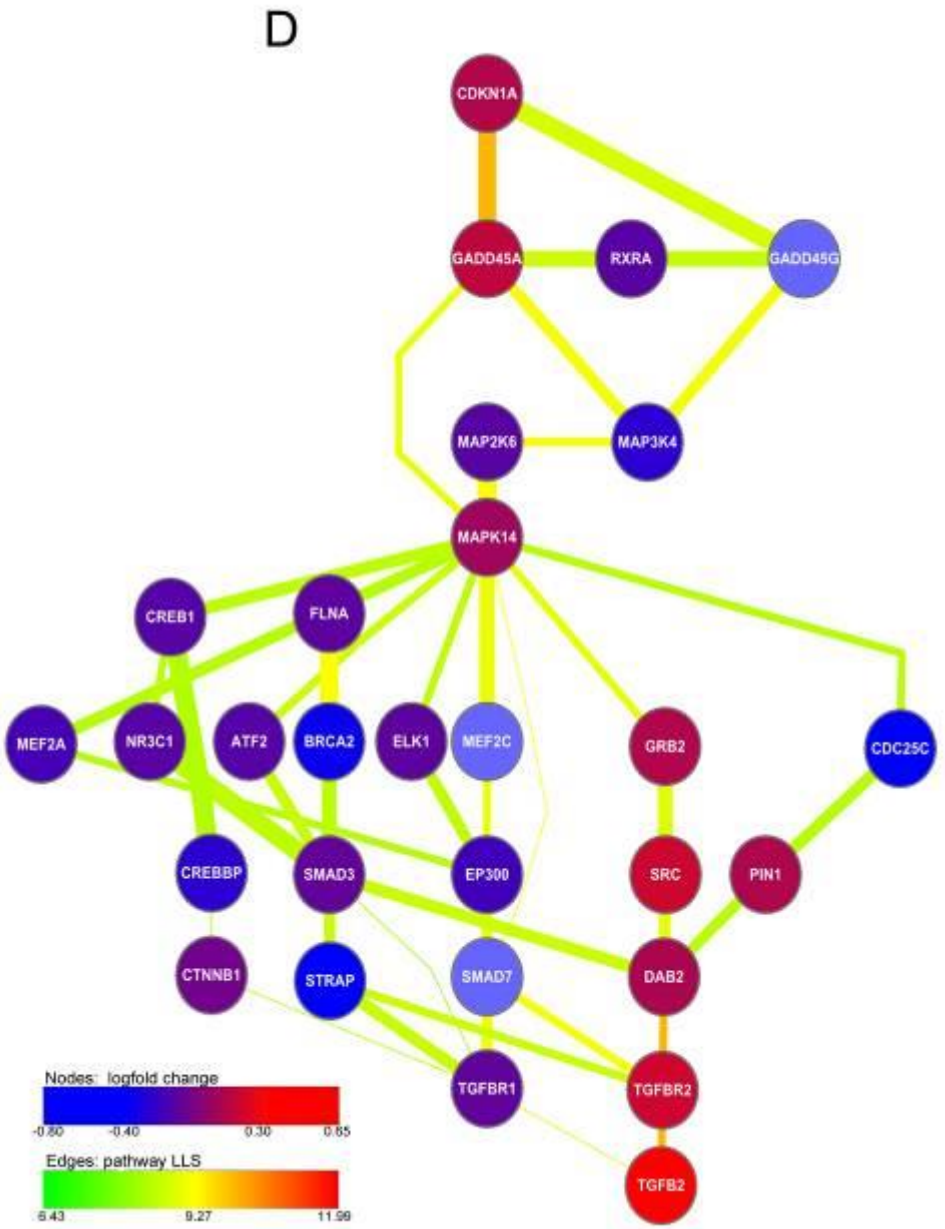


Multiple mechanisms:
- Telomere shortening
- Mitochondrial dysfunction
- Nuclear mutation
- Stochastic simulation

Sozou & Kirkwood 2001

Data

Mitochondrial Dysfunction Accounts for the Stochastic Heterogeneity in Telomere-Dependent Senescence
Passos et al, *PLoS Biology* 2007

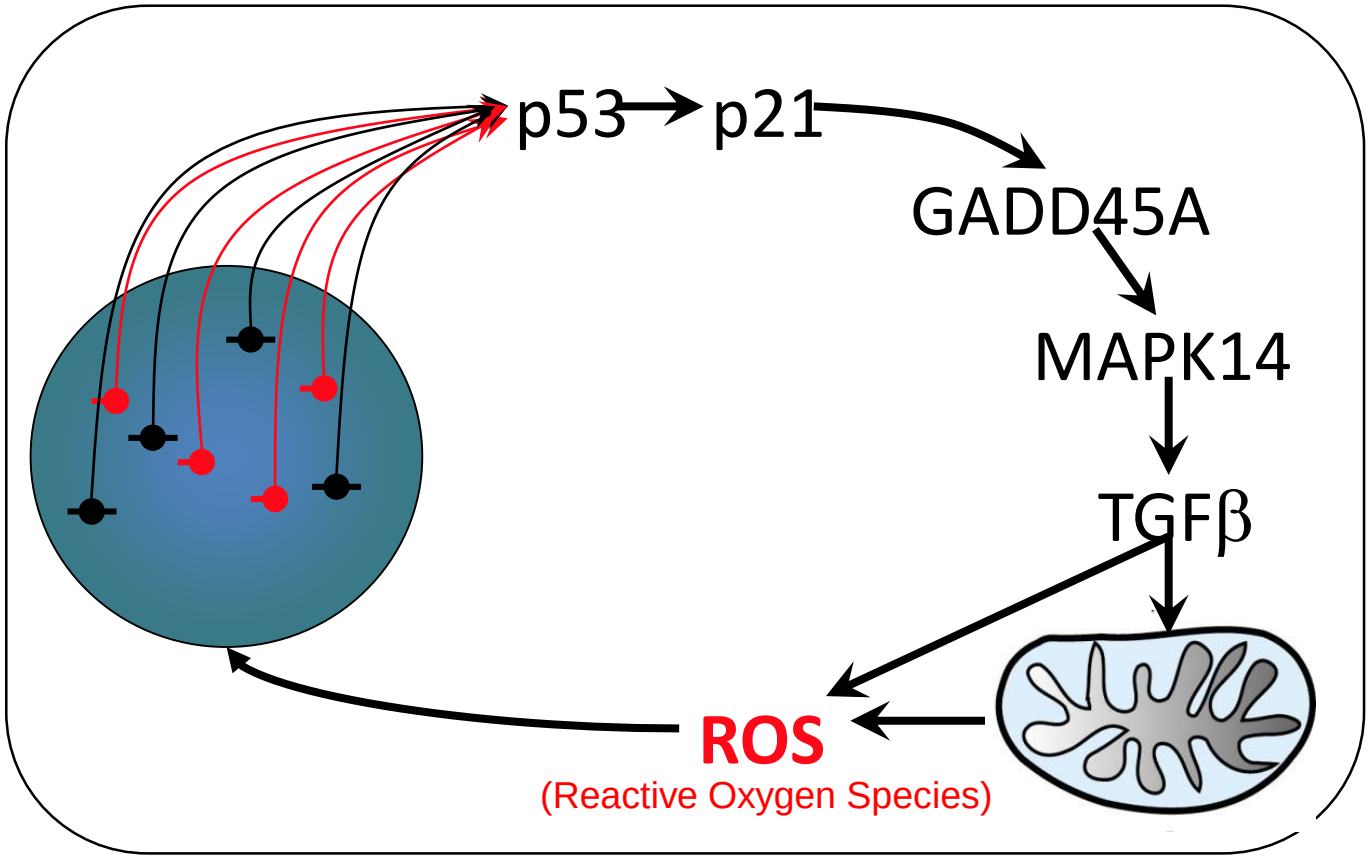


Combining *in-silico* interactome analysis and functional target gene inhibition, stochastic modelling and live cell imaging, we found that there exists a dynamic feedback loop that is triggered by molecular damage and which locks the cell into an actively maintained state of cellular senescence.

The essential feature of the loop is that long-term activation of the checkpoint gene CDKN1A (p21) induces mitochondrial dysfunction and production of reactive oxygen species (ROS) via serial signalling through GADD45-MAPK14(P38MAPK)–GRB2-TGFBR2-TGFb.

Passos et al *Mol Systems Biol* 2010

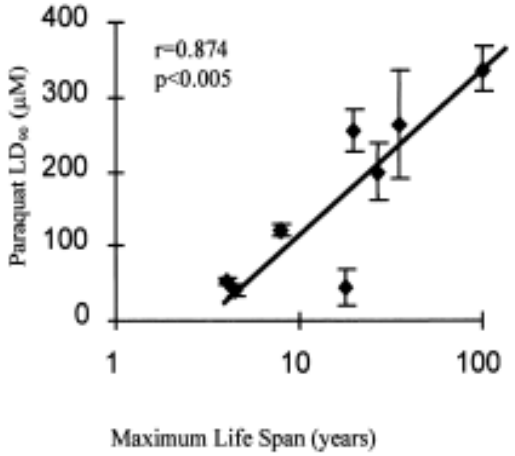
Cellular Responses to Damage – Senescence

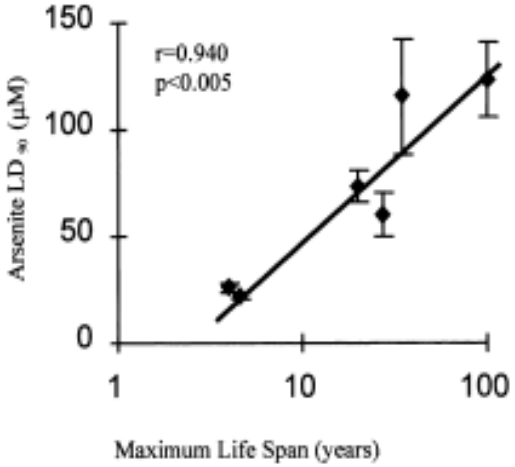


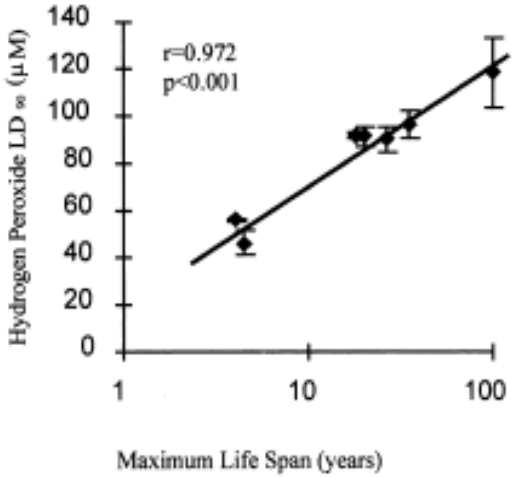
Senescence is a regulated response to damage mediated by a positive feedback loop between DNA damage and mitochondrial ROS generation. Passos et al. *Mol Sys Biol* 2010.

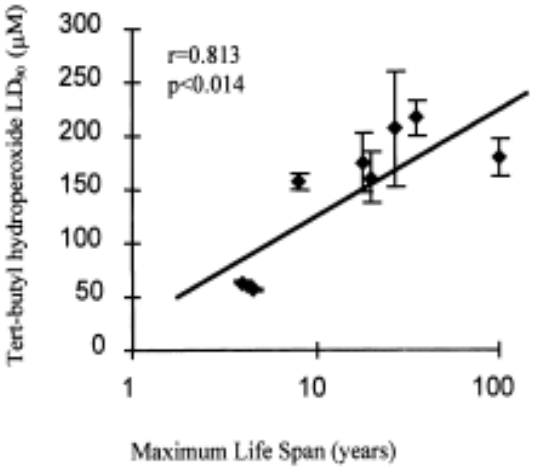
Cellular senescence is causally implicated in generating age-related phenotypes and removal of senescent cells can prevent or delay tissue dysfunction. Baker et al *Nature* 2011.

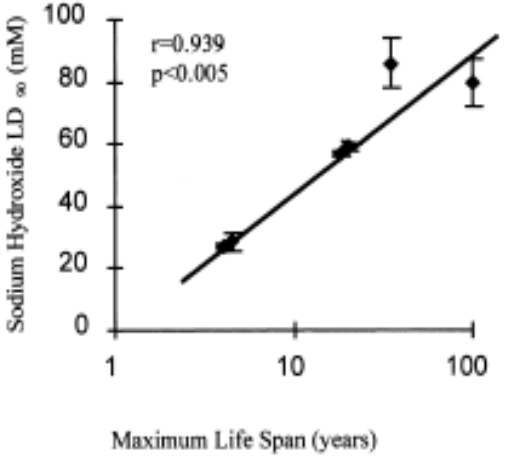
Correlation Between Cellular Stress Resistance and Mammalian Species Life Span





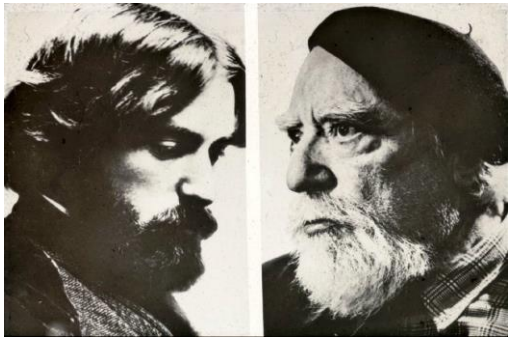






Kapahi, Boulton, Kirkwood *Free Rad Biol Med* 1999

Understanding the silent transformations of ageing



- Why and how does ageing occur?
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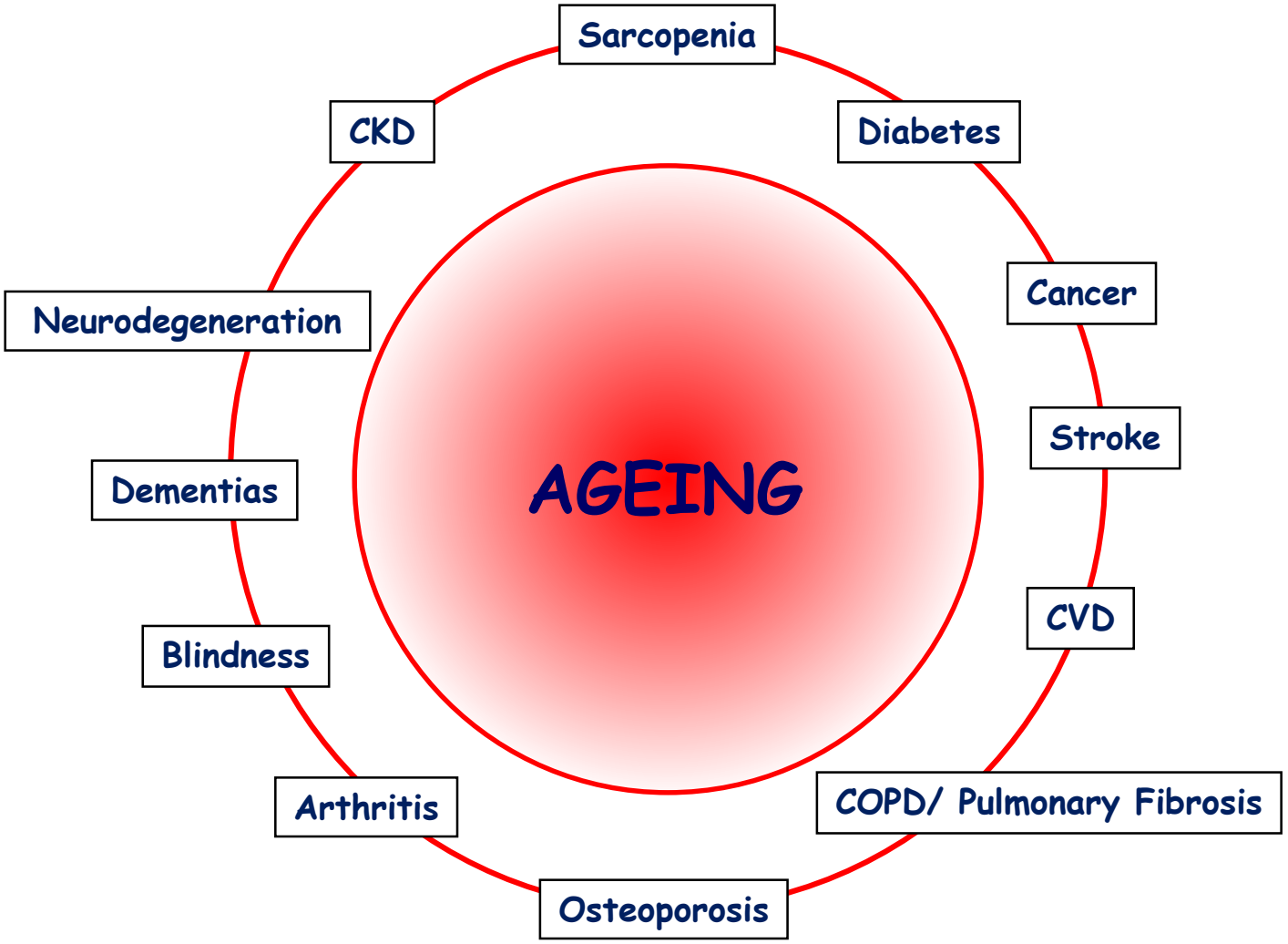
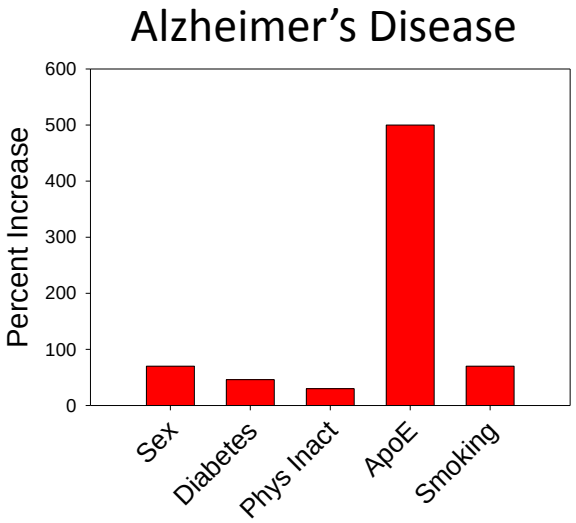
- Changing the mind-set

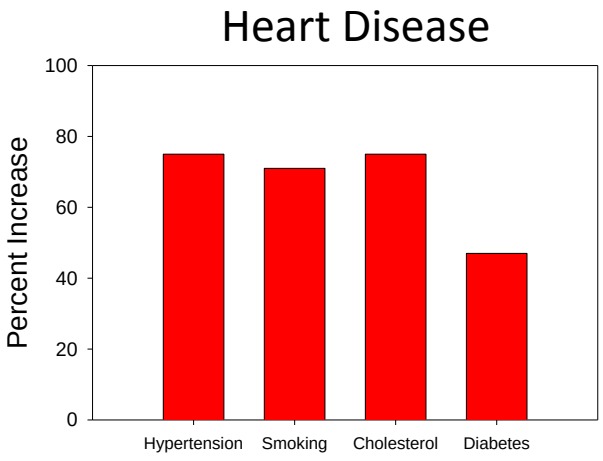
Intrinsic Ageing is the Primary Driver of Chronic Disease

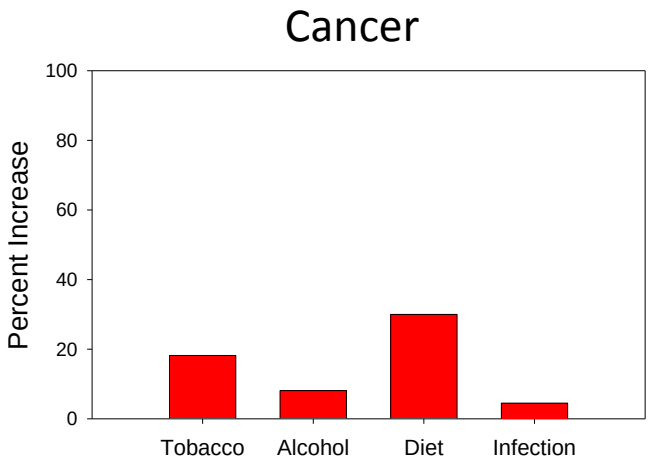


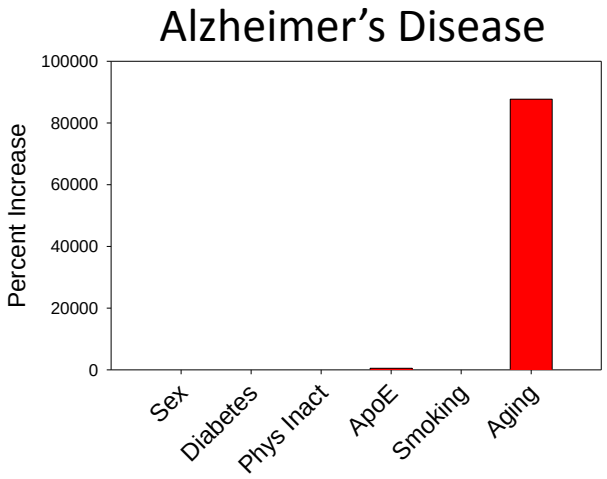
US National Institute on Aging

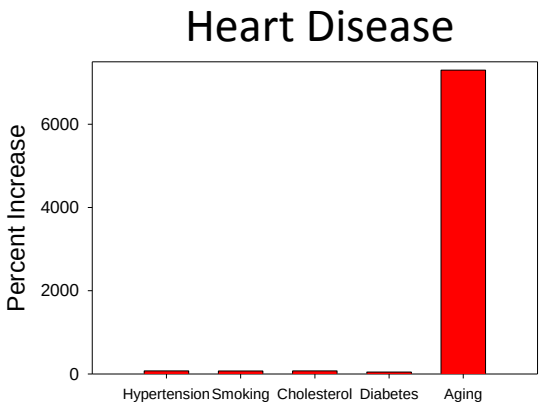
Risk Factors for Age-Related Diseases

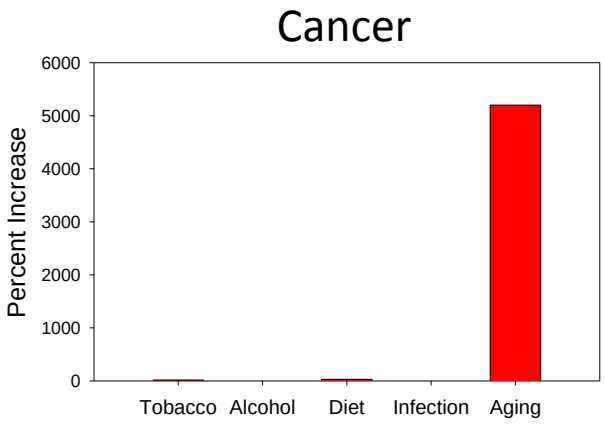






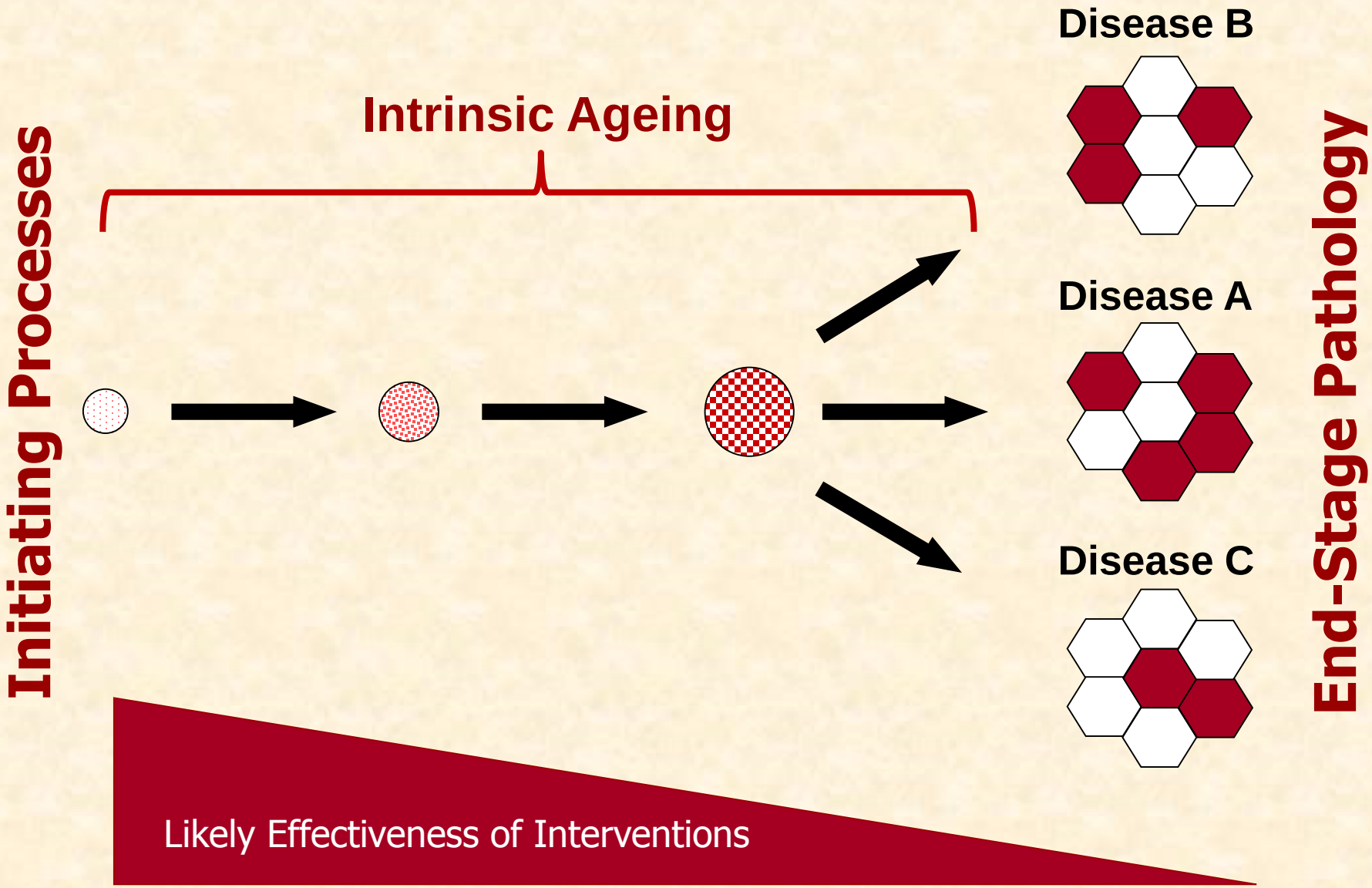






Intrinsic Ageing and Age-Related Disease

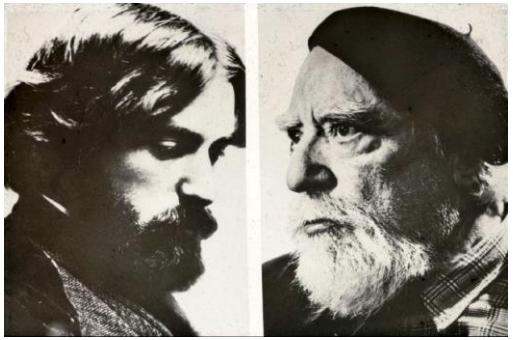
Accumulation of Molecular and Cellular Damage



Fundamental Mechanisms Shared by Intrinsic Ageing and Age-Related Chronic Diseases

- Macromolecular dysfunction
- Replicative senescence
- Apoptosis
- Stem cell dysfunction
- Inflammation (chronic, low-grade, sterile)

Understanding the silent transformations of ageing



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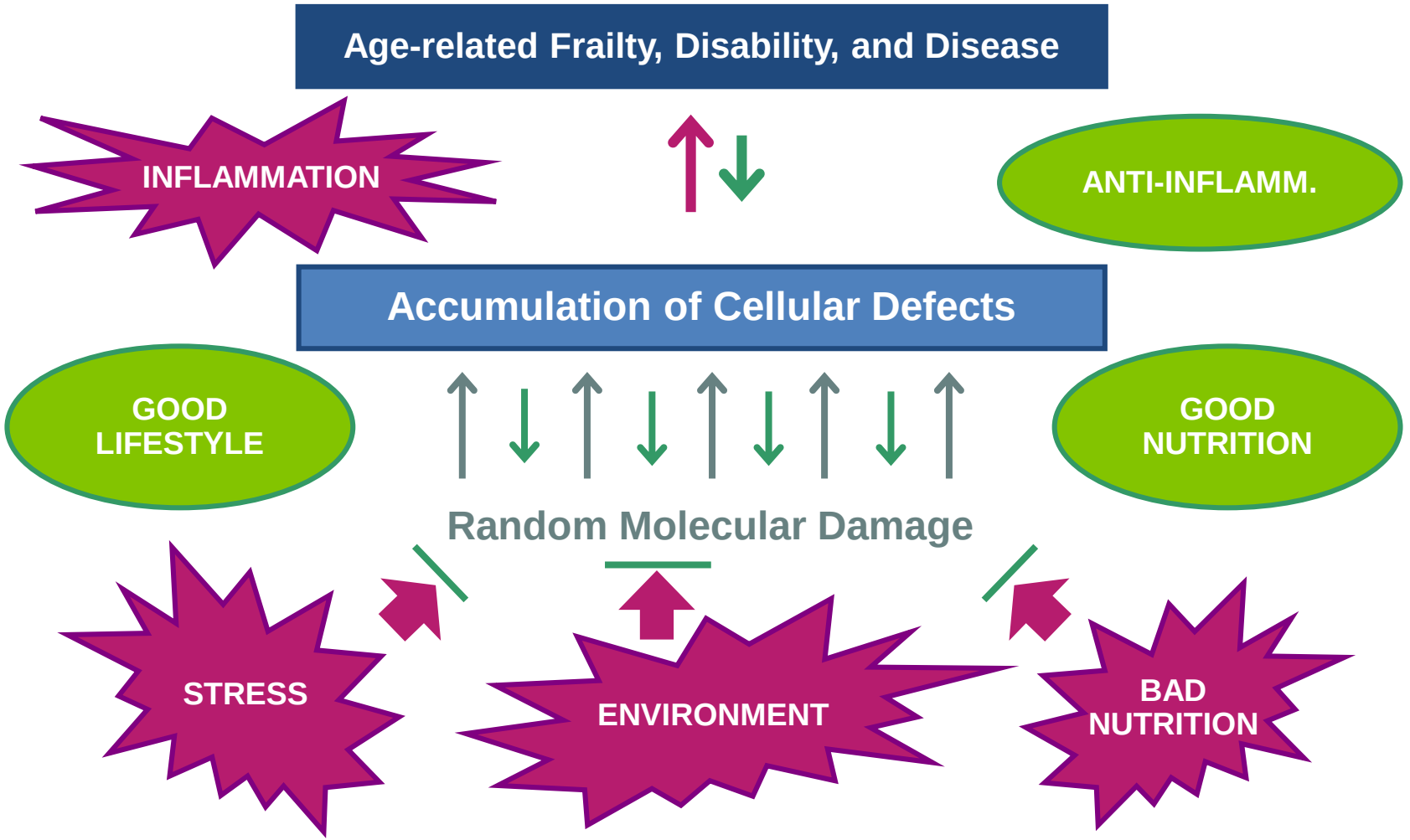
HUMAN AGEING AND ITS MALLEABILITY

Kirkwood *Cell* 2005



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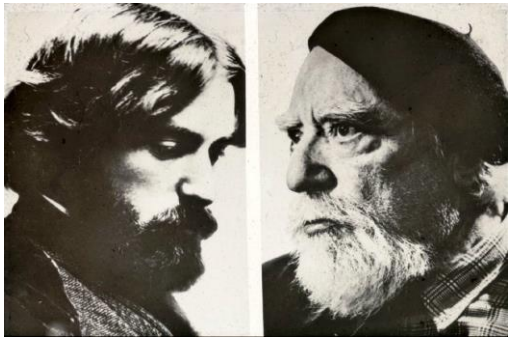

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Factors Influencing Health Trajectories in Old Age

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

Genetics of Human Longevity

Twin Studies	Coefficient of heritability
McGue et al (1993)	0.22
Herskind et al (1996)	0.25
Ljungquist et al (1998)	<0.33

►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.

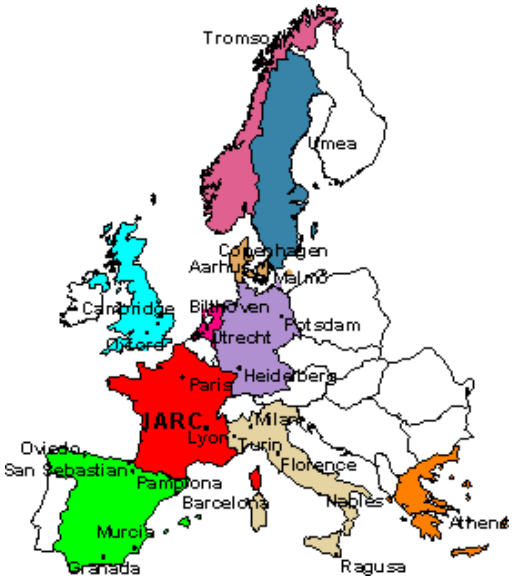
Schachter, Cohen, Kirkwood *Hum Genet* 1993
Kirkwood, Cordell, Finch *Trends Genet* 2011
Beekman et al *Aging Cell* 2013
Deelen et al *Hum Mol Genet* 2014

Nutrition and Survival: The EPIC-Ageing Study

76,707 men and women aged 60+

Followed for 7.5 years

Adherence to Mediterranean diet assessed on 10-point scale:
0 (poor)…9 (high)



2 unit increase in 'Mediterranean-ness' of diet results in 8% reduction of overall mortality

Trichopoulou A *et al.* (2005) *BMJ* 330, 991-997

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

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

Courtesy Prof Peter Gore/Prof Carol Jagger/ONS

Factors Influencing Health Trajectories in Old Age

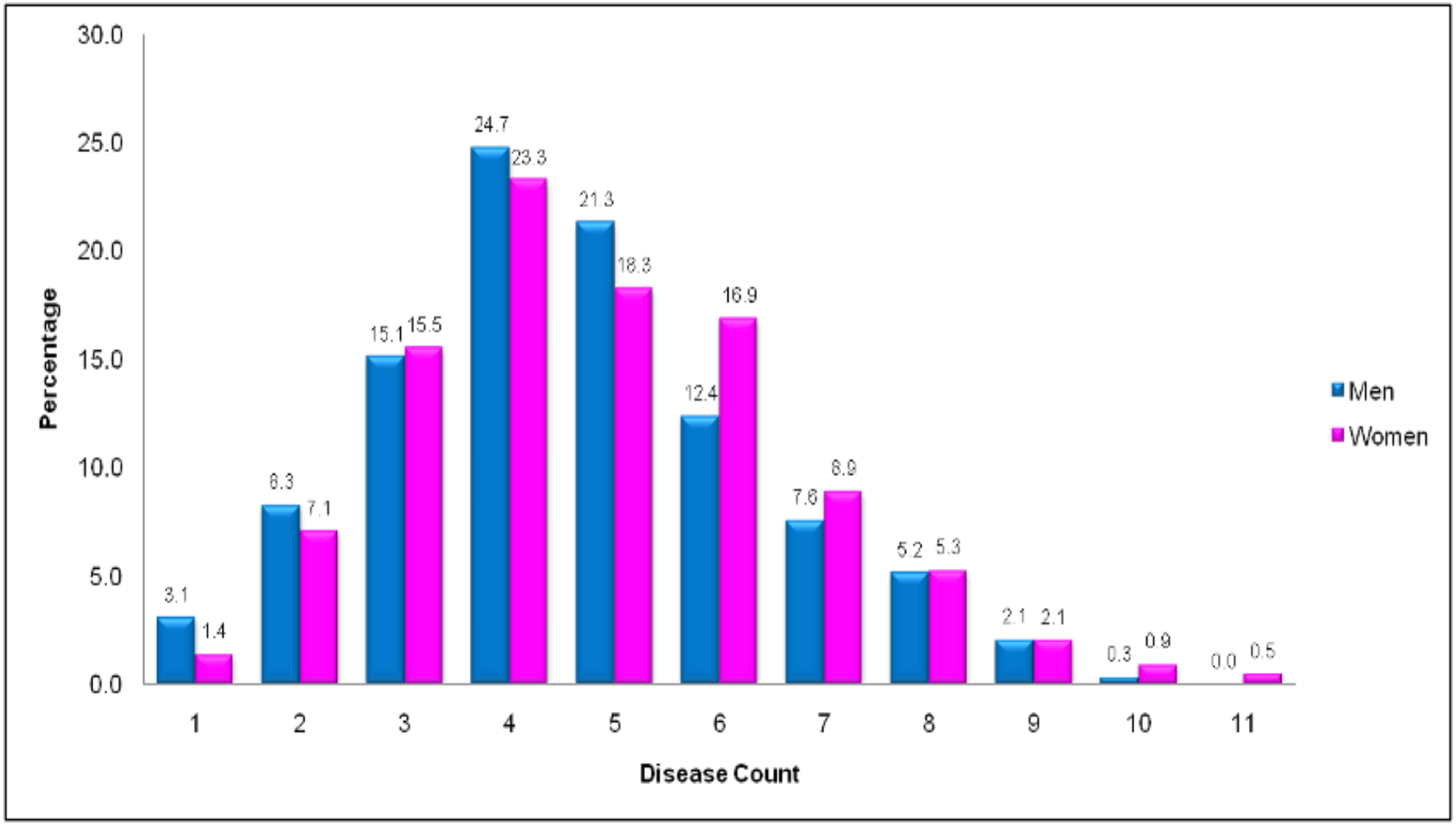
Newcastle 85+ Study; prospective study in 1000+ individuals born in 1921

Comprehensive study of the complex biological, medical and psychosocial factors affecting ageing trajectories of 85+ year olds.

Domains of assessment: health (nurse assessment and GP record review); cognitive and physical function; nutrition; activity; sleep; sensory function; psychology; socioeconomics; biological markers; genetics.

Exceptionally high rates of recruitment and retention through nurse-led development and refinement of procedures.

Multi-Morbidity is the Norm

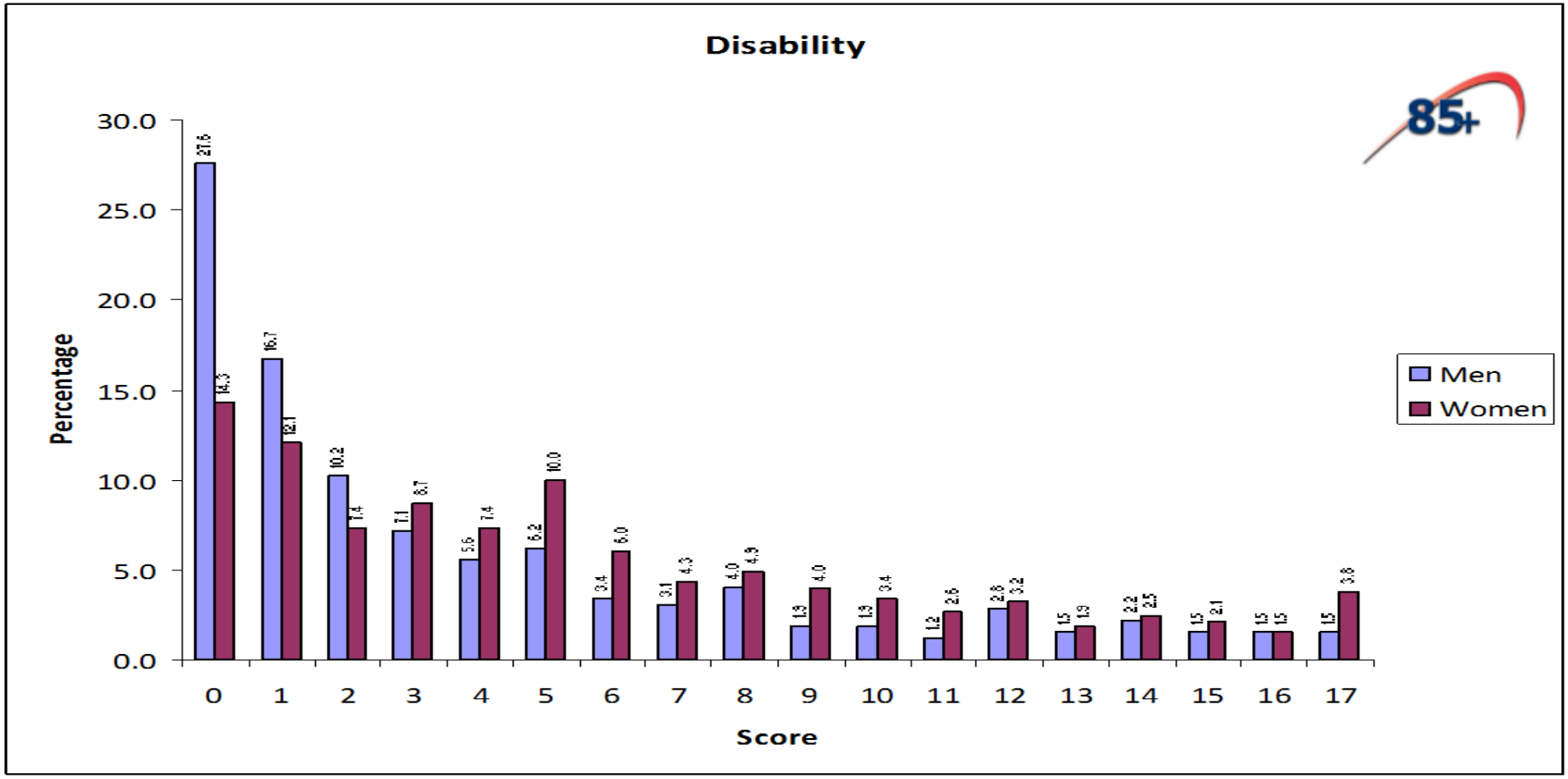


No one has perfect medical health at age 85.

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

Capability and Dependency



A quarter of men and a sixth of women have no important functional limitation at age 85.

Jagger et al *BMC Geriatrics* 2011

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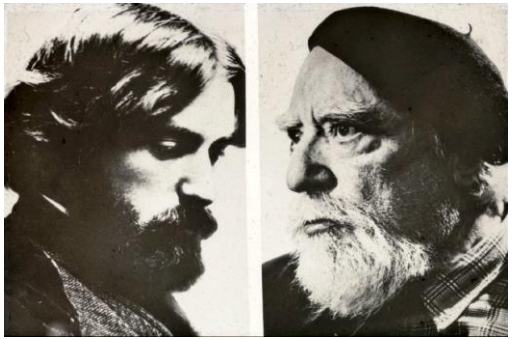


- Why and how does ageing occur?
- What is the relationship between ageing and disease?
- What explains the continuing increase in life expectancy?
- What accounts for the individuality of ageing?
- Changing the mind-set

OCTOBER 23 2005 'SUNDAY TELEGRAPH' (LEADER)

The bad news is we are living even longer

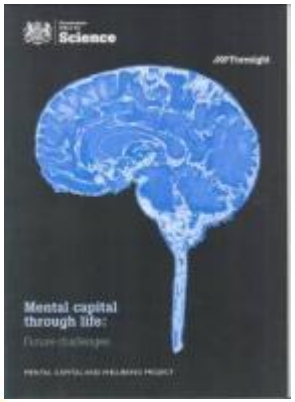
Billionaires to Live Forever?

Oracle founder Larry Ellison has proclaimed his wish to live forever and donated more than $430 million to anti-aging research. “Death has never made any sense to me,” he told his biographer, Mike Wilson. “How can a person be there and then just vanish, just not be there?”

Larry Page, who is now 41 and chief executive of Google, has made the biggest bet on longevity yet, founding Calico, short for California Life Company, a secretive anti-aging research center, with an investment of up to $750 million from Google.

Bill Gates has been very vocal in his praise of the generosity of Silicon Valley’s newly minted billionaires, but in January 2015 he expressed misgivings about their priorities. He wrote, “It seems pretty egocentric while we still have malaria and TB for rich people to fund things so they can live longer.”

The Life Course Trajectory of Mental Capital and Wellbeing



Mental Capital & Wellbeing

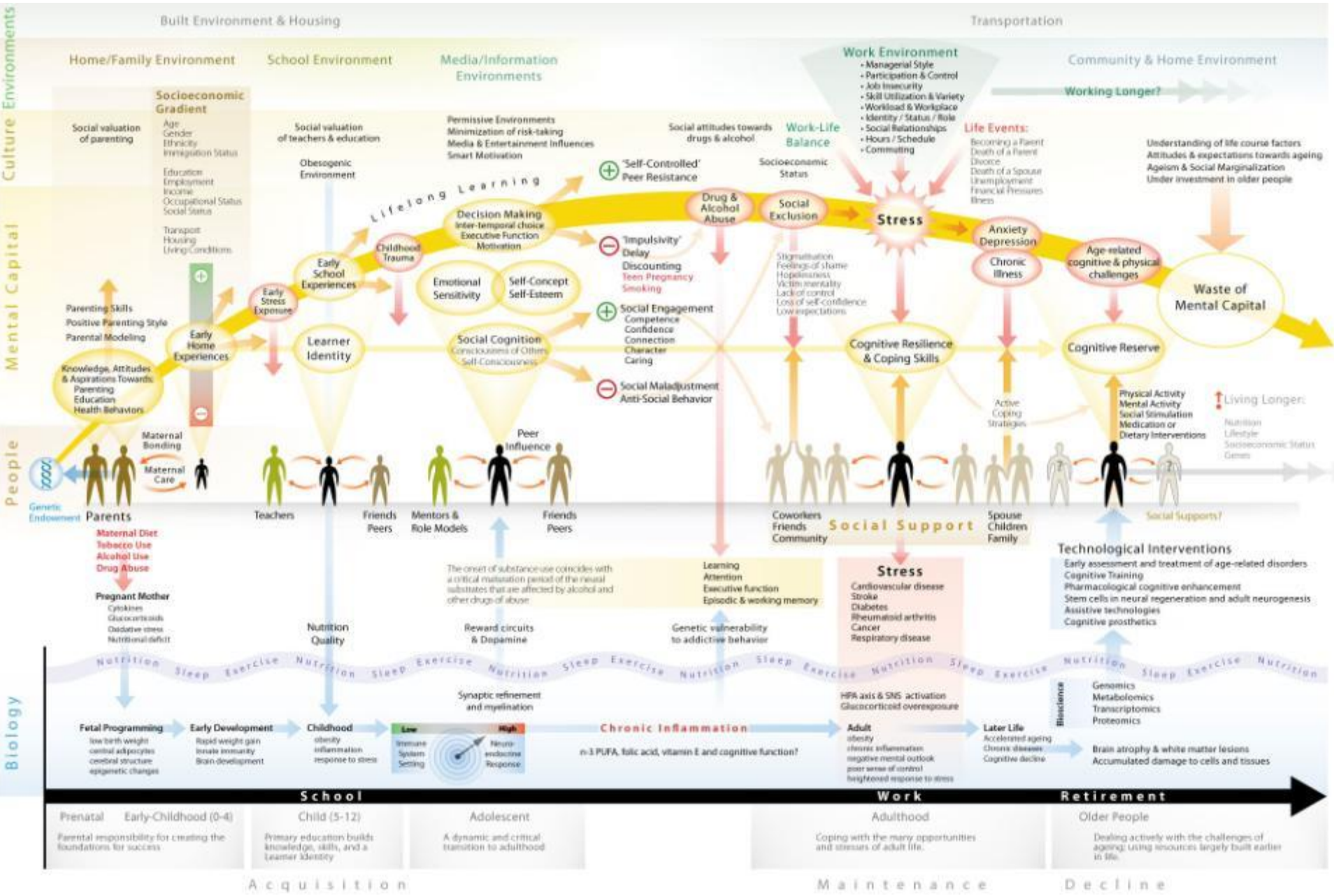
Childhood

Adulthood

Older

Lifestage

Government Office for Science - Foresight: Mental Capital and Wellbeing Project.
"Mental Capital Through Life: Future Challenges", Kirkwood et al 2008



Beddington et al. The mental wealth of nations. *Nature*. 2008;455:1057-60.

Key Questions and Implications

- Can we identify the precise factors contributing to the malleability of longevity and health in old age?
- Can we improve understanding of age-related multimorbidity?
- Can we use such knowledge further to promote health in old age and to reduce frailty and dependency?
- What mechanisms do we need to set in place to track trends in incidence of age-related diseases?

Common misconceptions about population ageing

- Old age is inevitably a period of poor quality existence
- Population ageing is the main cause of increased health costs
- Population ageing threatens dangerous growth in the size of the world's population
- Older people are an unsupportable economic burden

Thank you

Centre for Integrated Systems Biology of Ageing and Nutrition

Newcastle 85+ Study team

Institute for Ageing and Health (now NUIA)