Institute and Faculty of Actuaries

International Mortality and Longevity Symposium, September 2016

Can We Live Forever?

Tom Kirkwood

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

Newcastle University

UNIVERSITY OF COPENHAGEN

Robert Ettinger

1918-2011

Founder of the Immortalist Society

News Front Page
World
UK
England
Northern Ireland
Scotland
Wales
Business
Politics
Health
Education
Science & Environment
Technology
Entertainment
Also in the news
Video and Audio
Have Your Say
Magazine
In Pictures
Country Profiles
Special Reports
RELATED BBC SITES
SPORT
WEATHER
BBC NEWSROUND
ON THIS DAY
EDITORS' BLOG
Languages
NEWYDDION

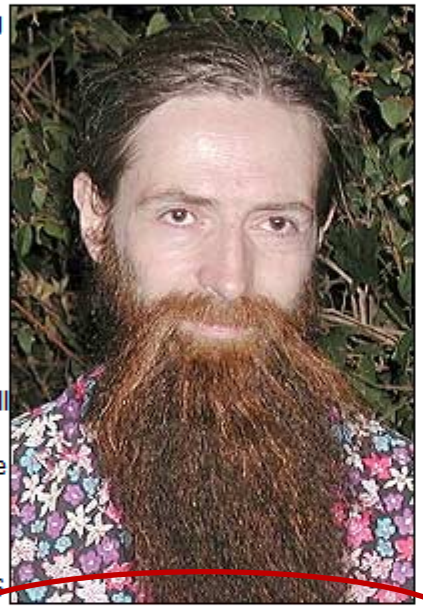
Last Updated: Friday, 3 December, 2004, 00:01 GMT

E-mail this to a friend | Printable version

'We will be able to live to 1,000'

By Dr Aubrey de Grey
University of Cambridge

Life expectancy is increasing in the developed world. But Cambridge University geneticist Aubrey de Grey believes it will soon extend dramatically to 1,000. Here, he explains why.



Aubrey de Grey: "The first person to live to 1,000 might be 60 already"

Ageing is a physical phenomenon happening to our bodies, so at some point in the future, as medicine becomes more and more powerful, we will inevitably be able to address ageing just as effectively as we address many diseases today.

I claim that we are close to that point because of the SENS (Strategies for Engineered Negligible Senescence) project to prevent and cure ageing.

It is not just an idea: it's a very detailed plan to repair all the types of molecular and cellular damage that happen to us over time.

And each method to do this is either already working in a preliminary form (in clinical trials) or is based on technologies that already exist and just need to be combined.

The Ageing Revolution — In Depth

KEY STORIES

Burden on society?
We're living longer and doing more so why the gloomy headlines?

- Will we still be working at 70?
- Destined for a frail or fit old age?
- 'Why ageism must be eradicated'

Population shift
Interactive graphic: See how the UK ages 1901-2051

FEATURES

- 'We will be able to live to 1,000'
- Notions of beauty may change
- Mature fans keep on rocking
- Learning in the third age
- Later love - starting over at 50

VIDEO AND AUDIO

Watch 'Elder abuse' concern

HAVE YOUR SAY

- Ageing Britain: Your views

SEE ALSO:

- 'Don't fall for the cult of immortality'
  03 Dec 04 | UK
- Humans 'will live to age of 150'
  22 Oct 04 | Science/Nature
- The secrets of long life revealed?

See also:
The Actuary
April 2016

First things first

- Do we know why ageing occurs?
- Do we understand what determines longevity?
- What is already happening to human longevity?
- What accounts for the individuality of ageing?
- What does the latest research tell us about possible interventions?
- What are the key challenges for extending the human healthspan?

What's the Point of Ageing?

- Nature's way of creating living space for the next generation.
- A means to ensure the turnover of generations and accelerate adaptation to changing environment.

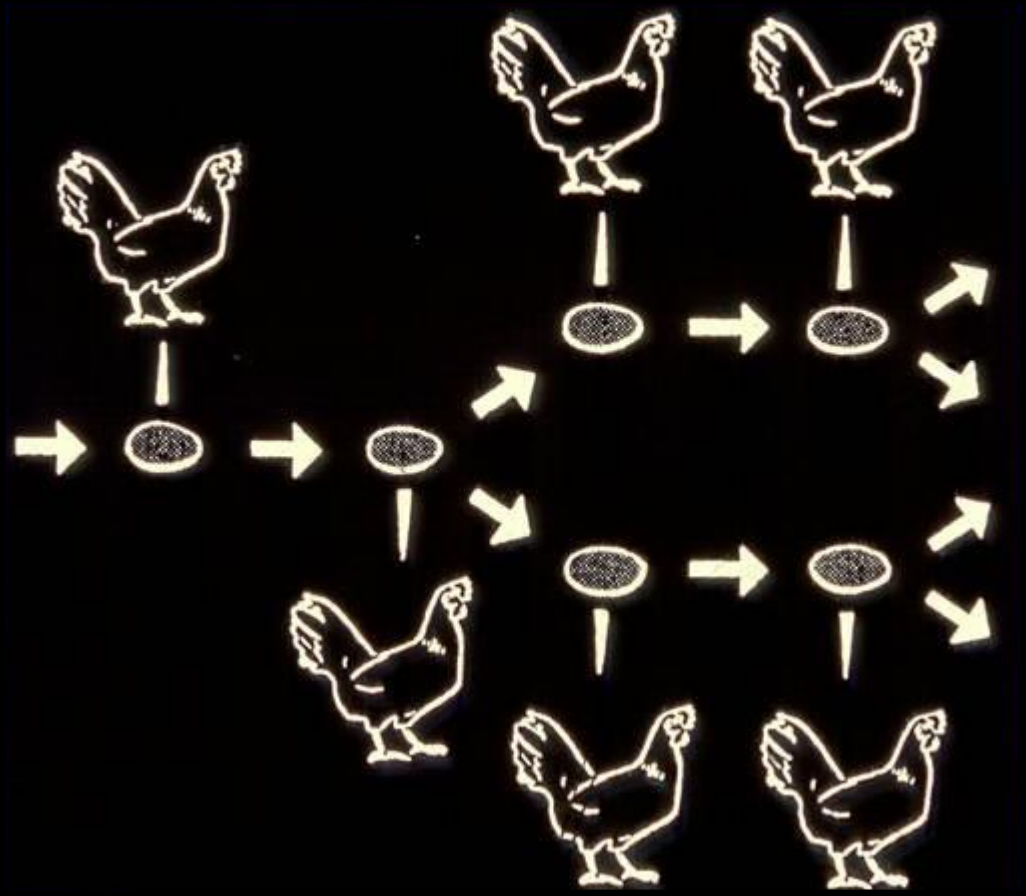
➢ If true, such ideas would suggest ageing is programmed.

BUT:

- Relatively few animals reach 'old age' in the wild.
- The gradual, messy and variable nature of ageing does not look to be an act programmed self-destruction.
- The quantitative arguments don't add up.

Kirkwood & Melov *Current Biology* 2011
Kowald & Kirkwood *Aging Cell* 2016

Immortal Germ-Line – Mortal Soma

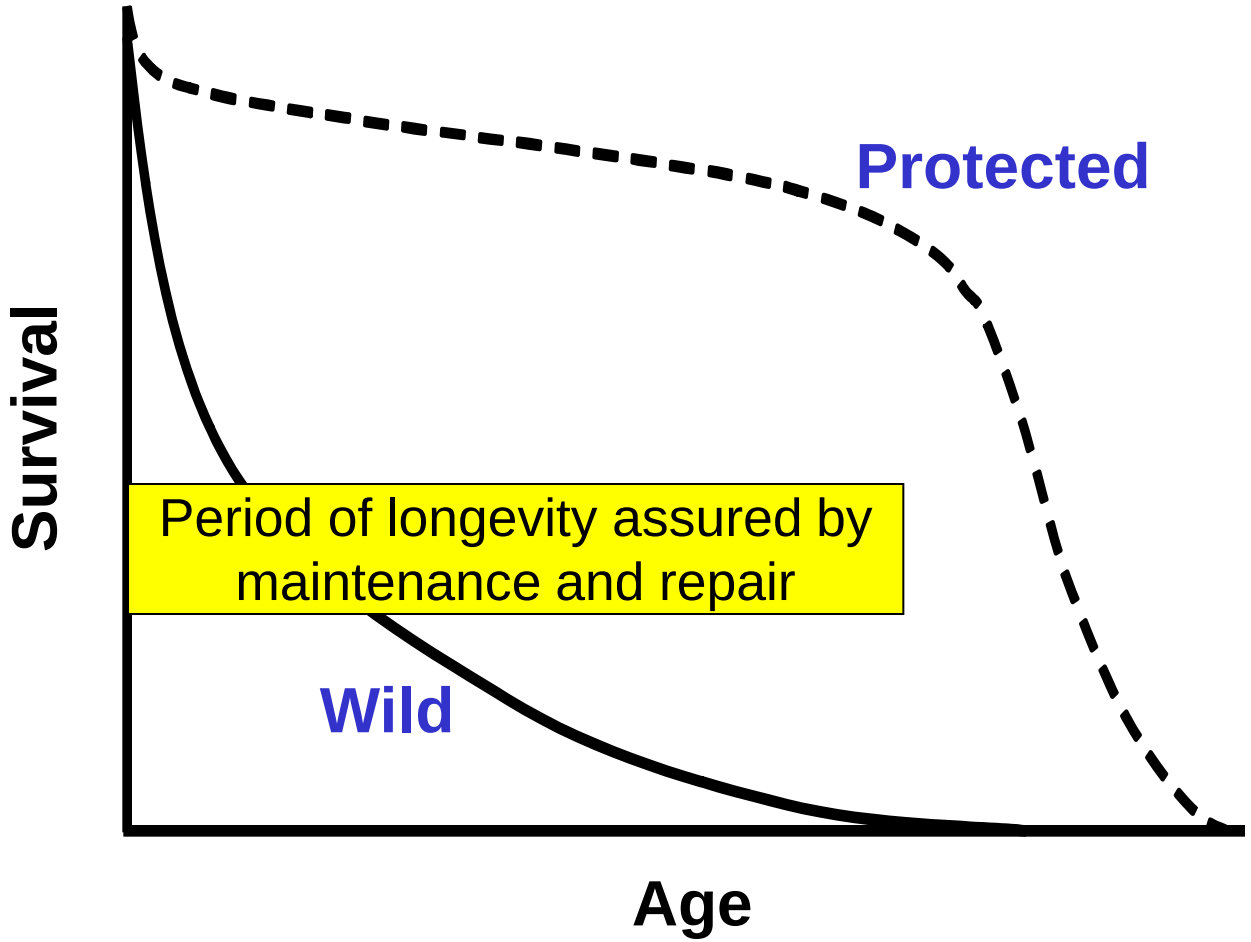


August Weismann

Natural selection dictates that organisms should optimise their allocation of metabolic resources

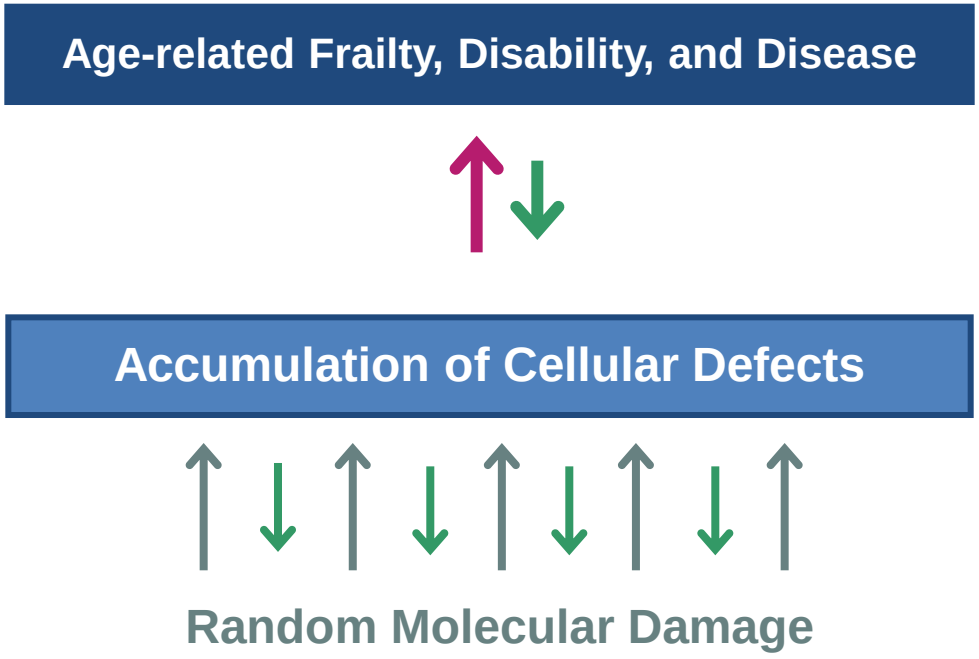
Kirkwood (1981) in *Physiological Ecology: An Evolutionary Approach to Resource Use* (eds Townsend & Calow)

DISPOSABLE SOMA THEORY



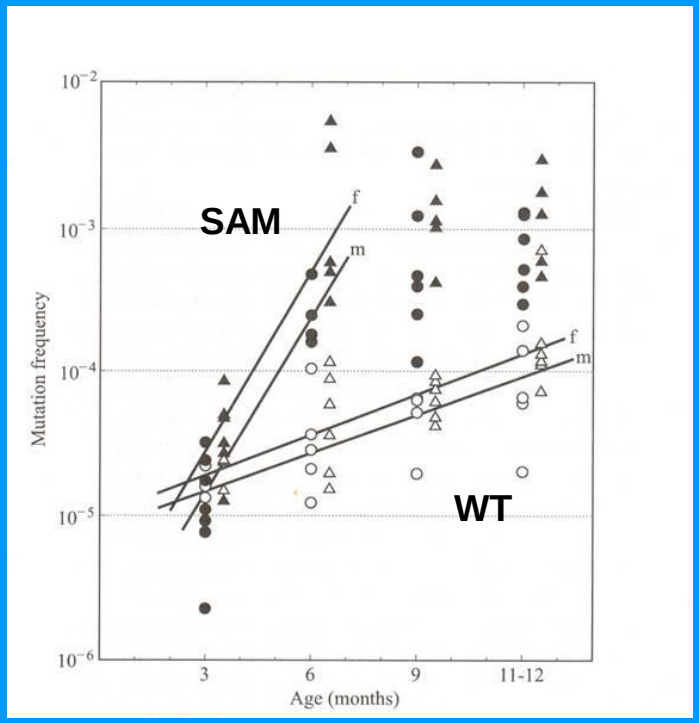
Kirkwood *Nature* 1977

THE AGEING PROCESS



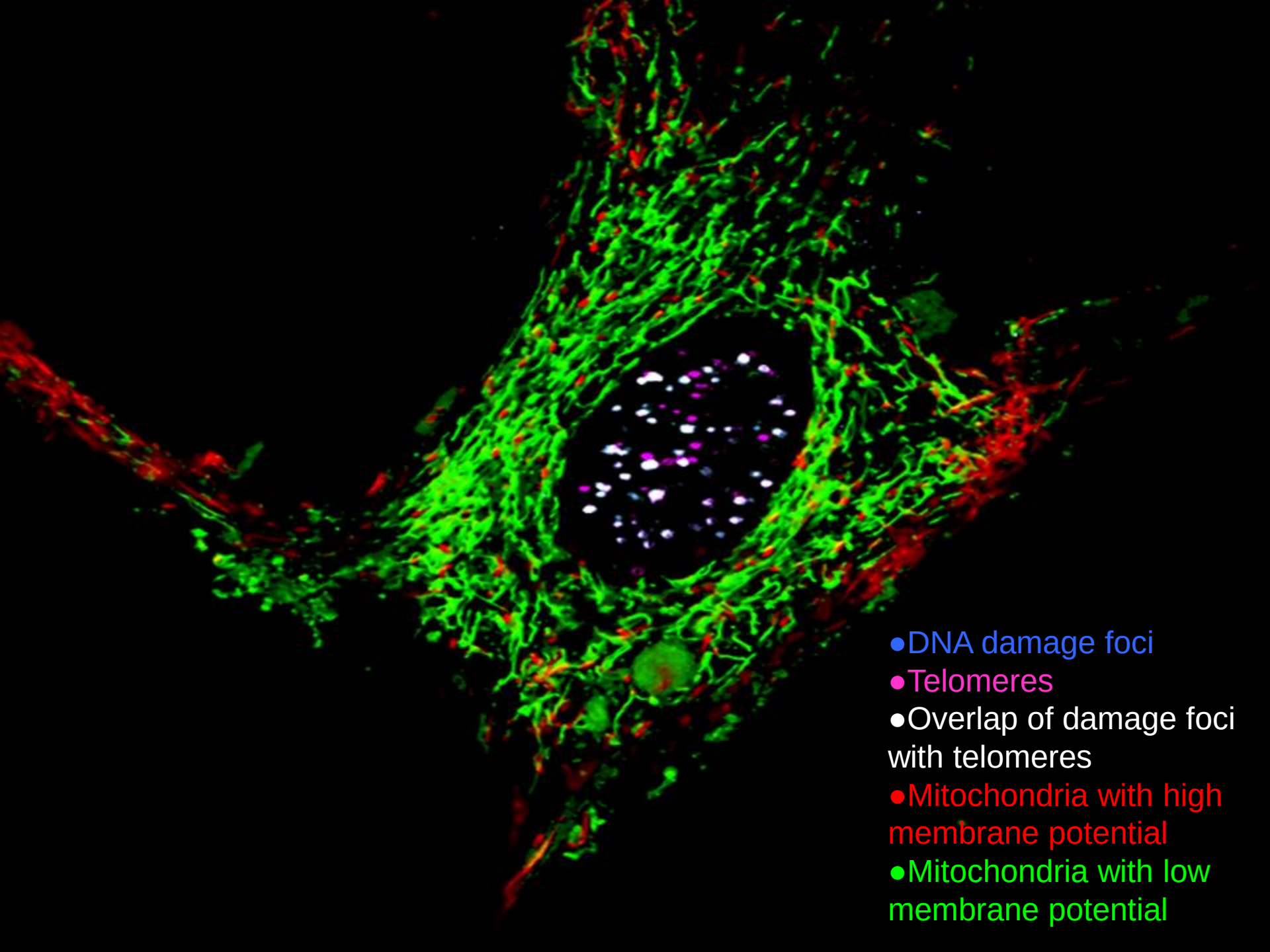
Damage Accumulates From Day One

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


●DNA damage foci
●Telomeres
●Overlap of damage foci with telomeres
●Mitochondria with high membrane potential
●Mitochondria with low membrane potential

First things first

- Do we know why ageing occurs?
- Do we understand what determines longevity?
- What is already happening to human longevity?
- What accounts for the individuality of ageing?
- What does the latest research tell us about possible interventions?
- What are the key challenges for extending the human healthspan?


31 y

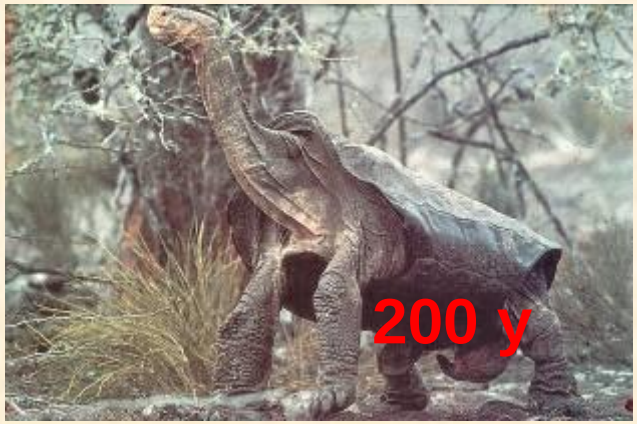

122 y

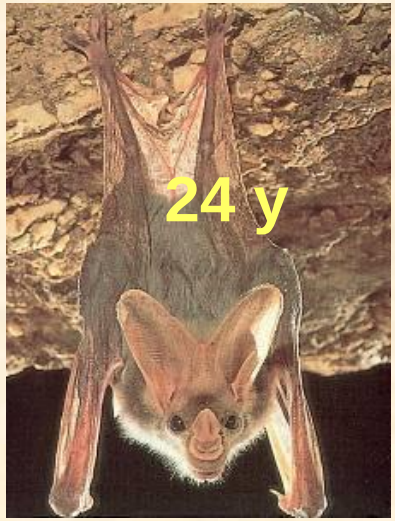

3 m – 10 y


21 days

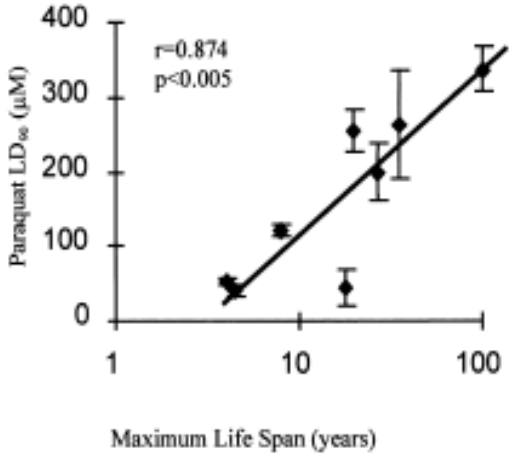

>2000 y

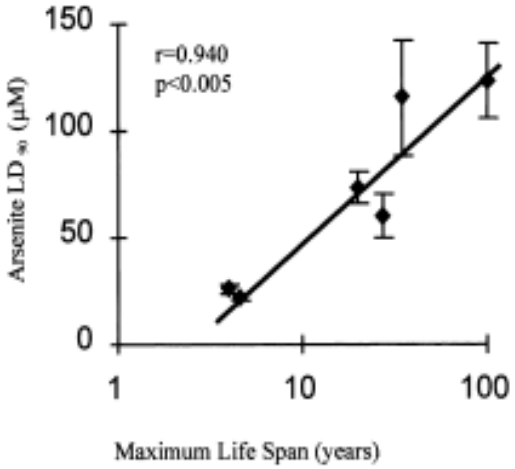

28 y
3 y

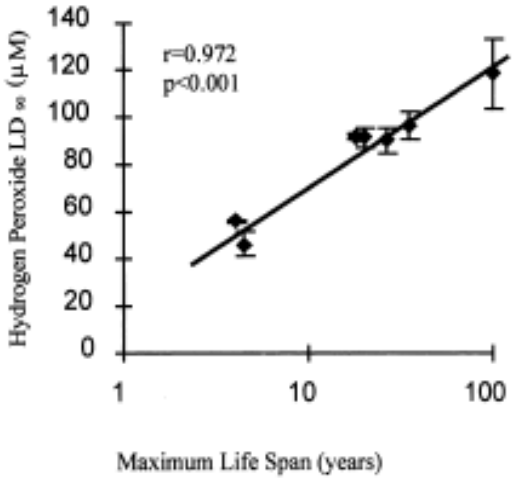

200 y

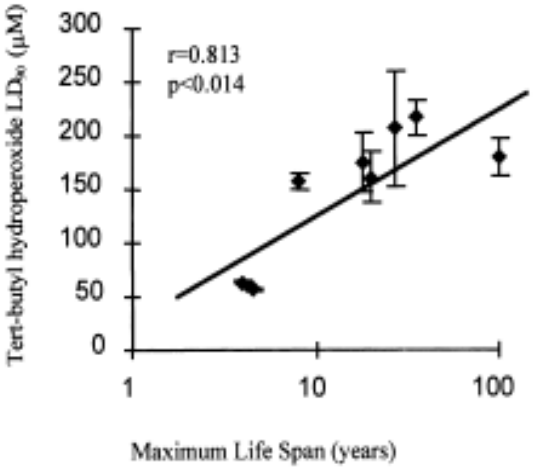

24 y

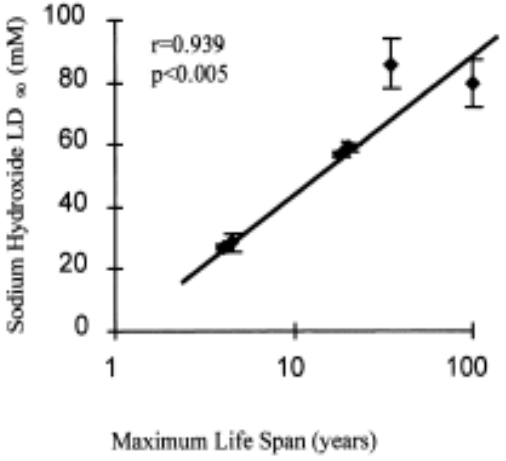
Correlation Between Cellular Stress Resistance and Mammalian Species Life Span





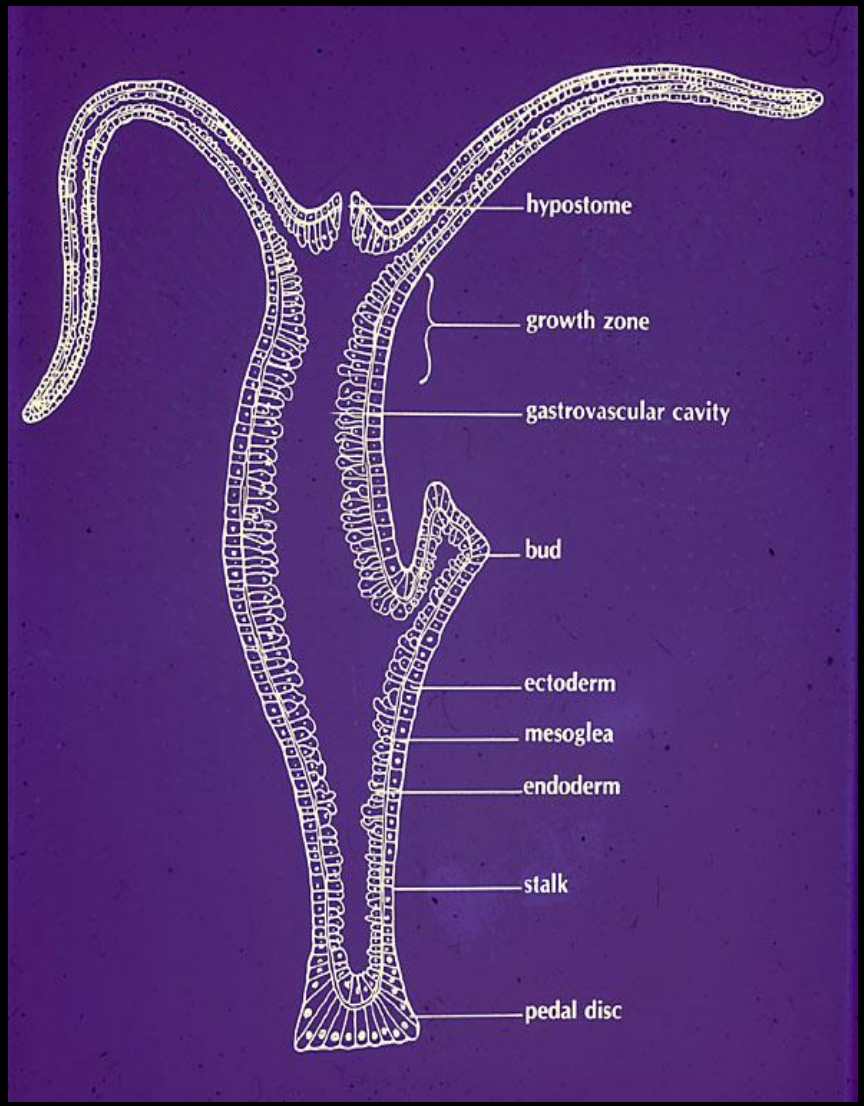






Kapahi, Boulton, Kirkwood *Free Rad Biol Med* 1999

An Exception Which Proves The Rule - ‘Immortal’ Hydra

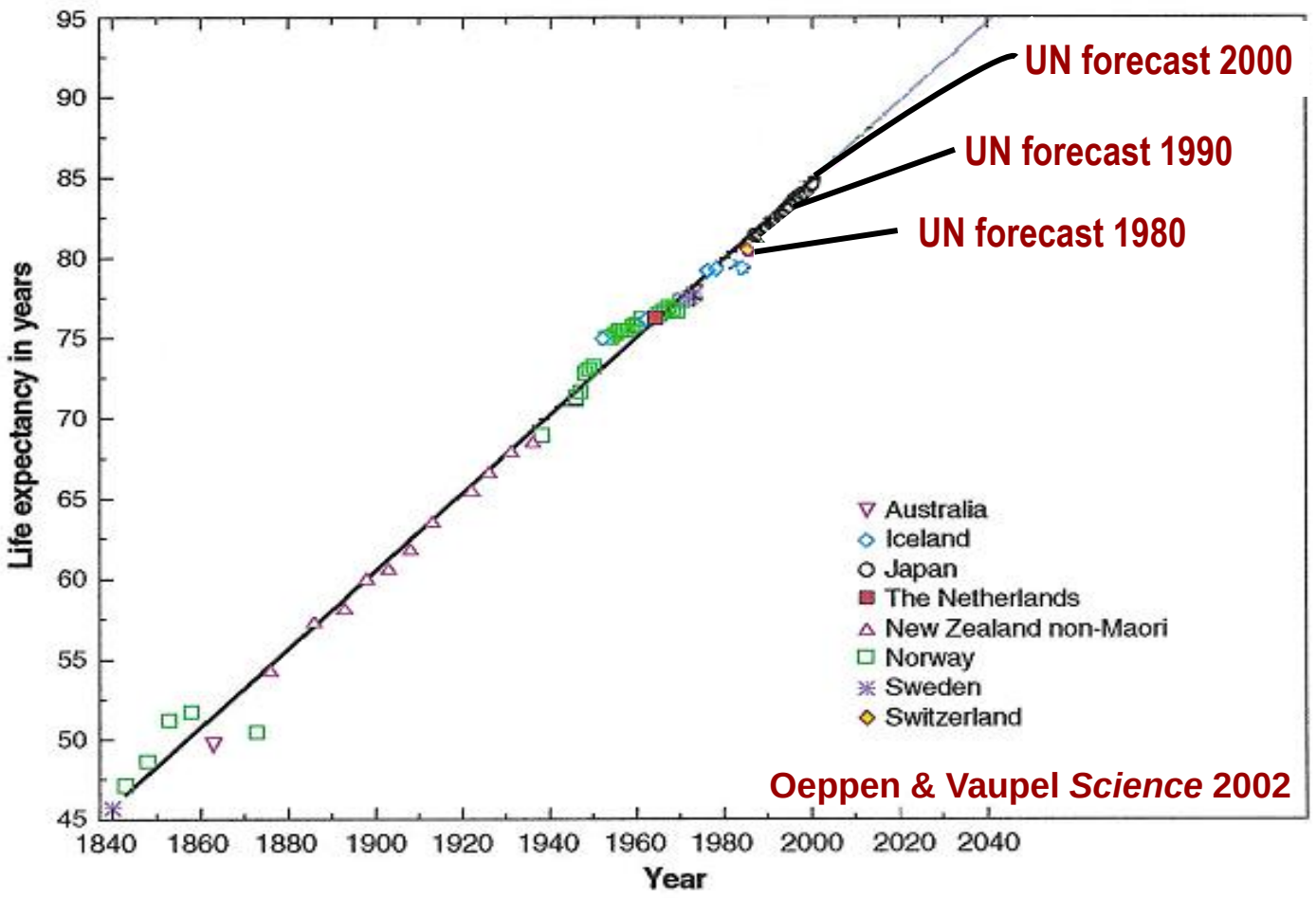


- Hydra can reproduce sexually but mainly reproduce by budding
- Any part can regenerate the whole
- Germ cells permeate the entire structure
- Therefore, Hydra has no true soma to be disposable

First things first

- Do we know why ageing occurs?
- Do we understand what determines longevity?
- What is already happening to human longevity?
- What accounts for the individuality of ageing?
- What does the latest research tell us about possible interventions?
- What are the key challenges for extending the human healthspan?

The Increase in Human Life Expectancy

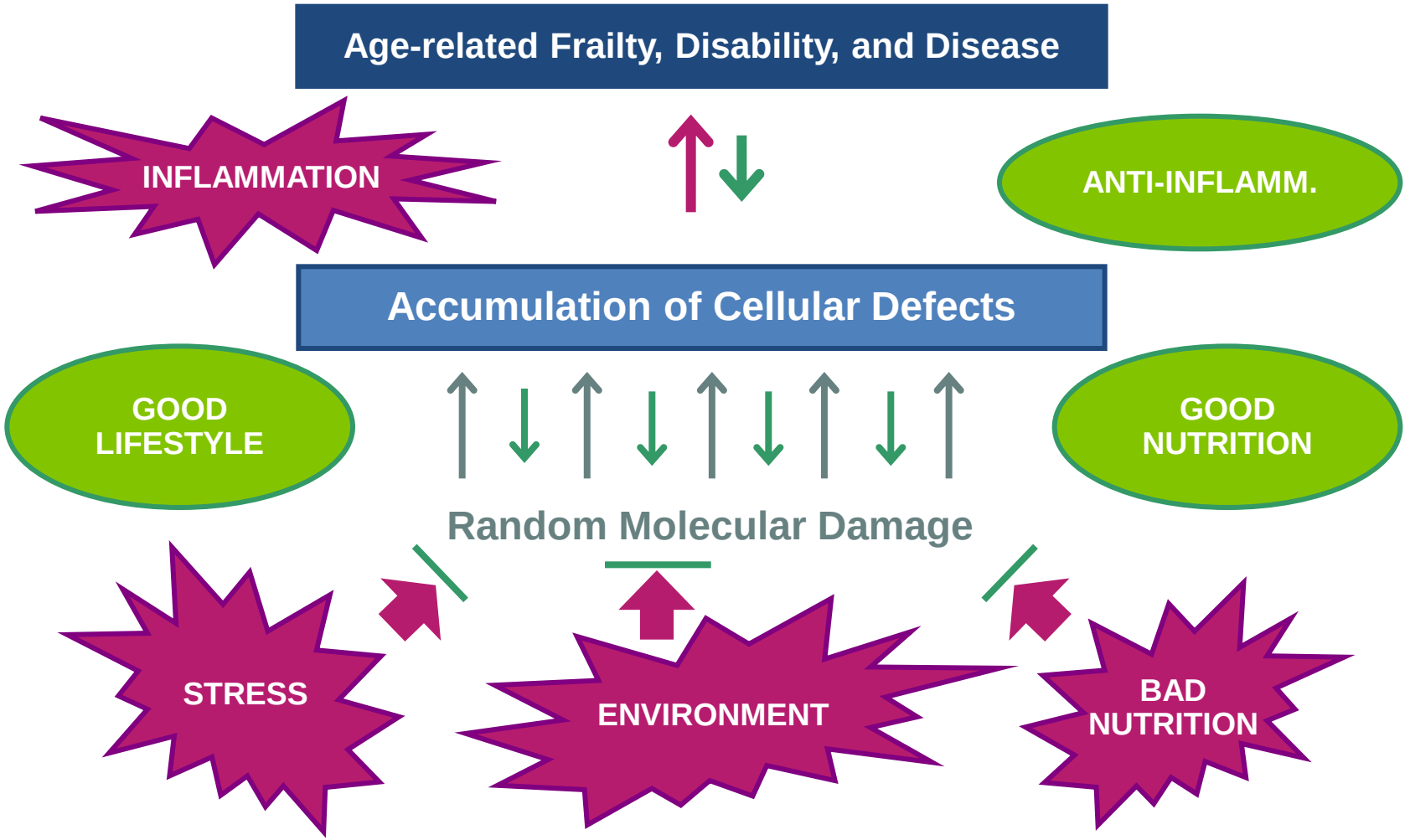


Declining early/mid-life mortality

Declining later-life mortality

HUMAN AGEING AND ITS MALLEABILITY

Kirkwood *Cell* 2005



First things first

- Do we know why ageing occurs?
- Do we understand what determines longevity?
- What is already happening to human longevity?
- What accounts for the individuality of ageing?
- What does the latest research tell us about possible interventions?
- What are the key challenges for extending the human healthspan?

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.

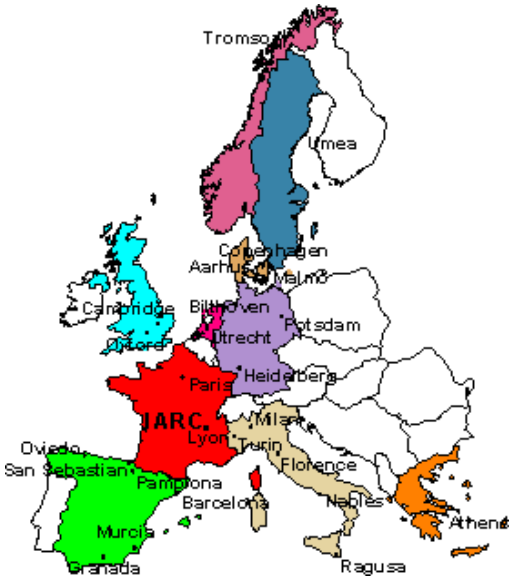
Schachter, Cohen, Kirkwood *Hum Genet* 1993
Kirkwood, Cordell, Finch *Trends Genet* 2011
Beekman et al *Aging Cell* 2013
Deelen et al *Hum Mol Genet* 2014

Nutrition and Survival: The EPIC-Ageing Study

76,707 men and women aged 60+

Followed for 7.5 years

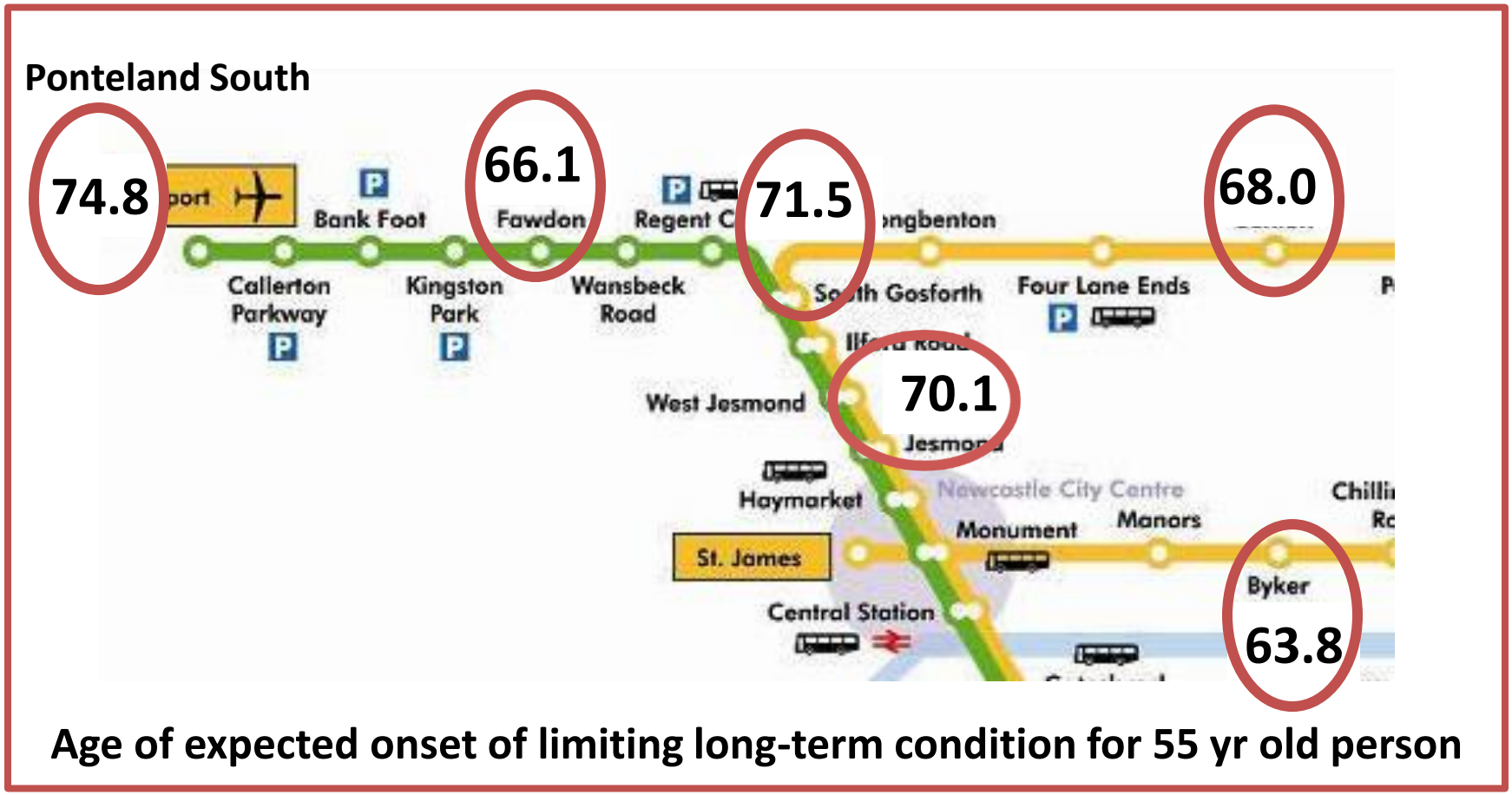
Adherence to Mediterranean diet assessed on 10-point scale:
0 (poor)…9 (high)



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

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

The ‘social gradient’ in healthy life expectancy



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

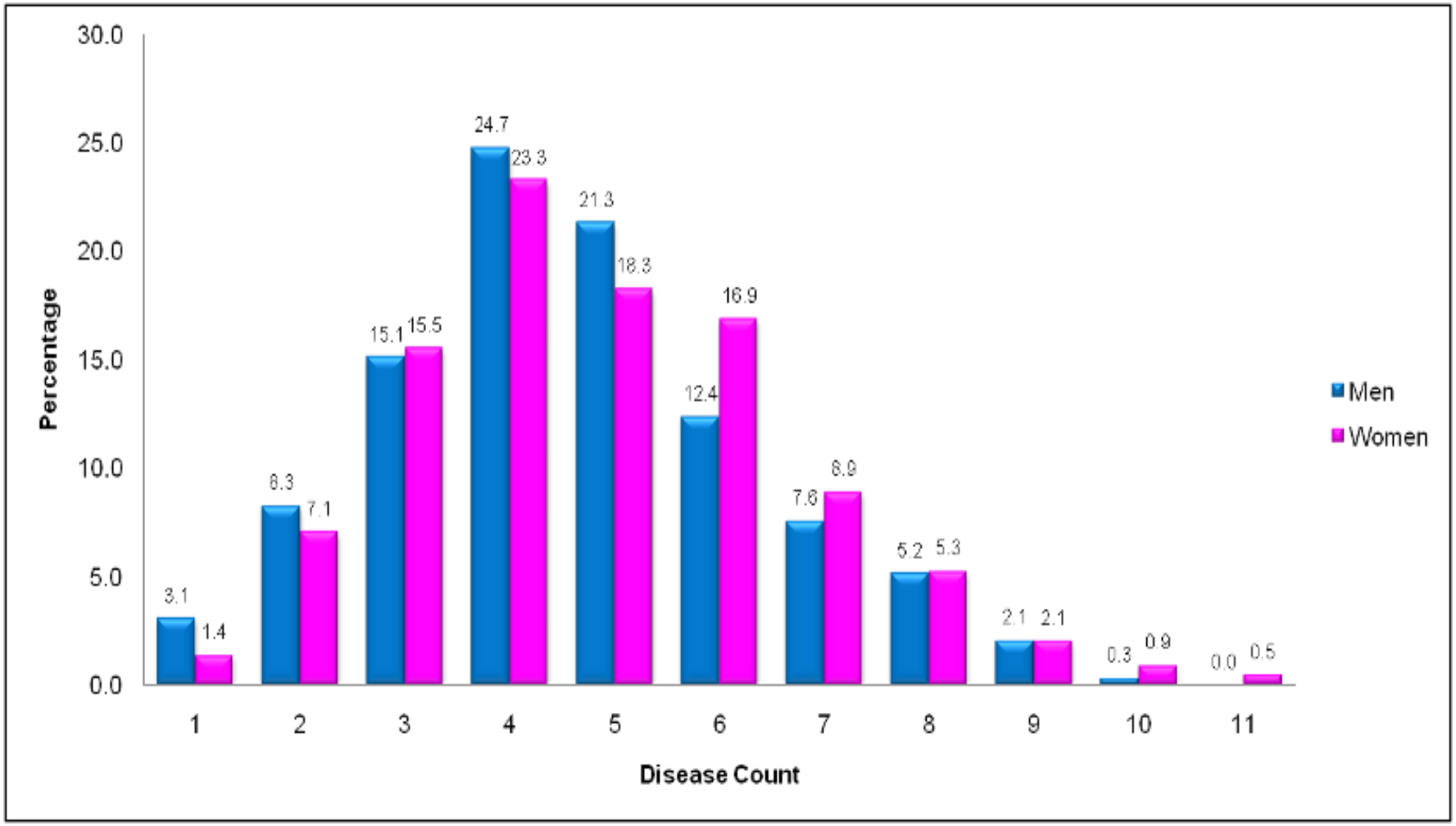
Courtesy Prof Peter Gore/Prof Carol Jagger/ONS

Complex Factors Influence Individual Ageing Trajectories

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

Newcastle 85+ Study; a prospective study in 1041 individuals all born in 1921 of the biological, clinical and psychosocial factors associated with healthy aging.

Multi-Morbidity is the Norm

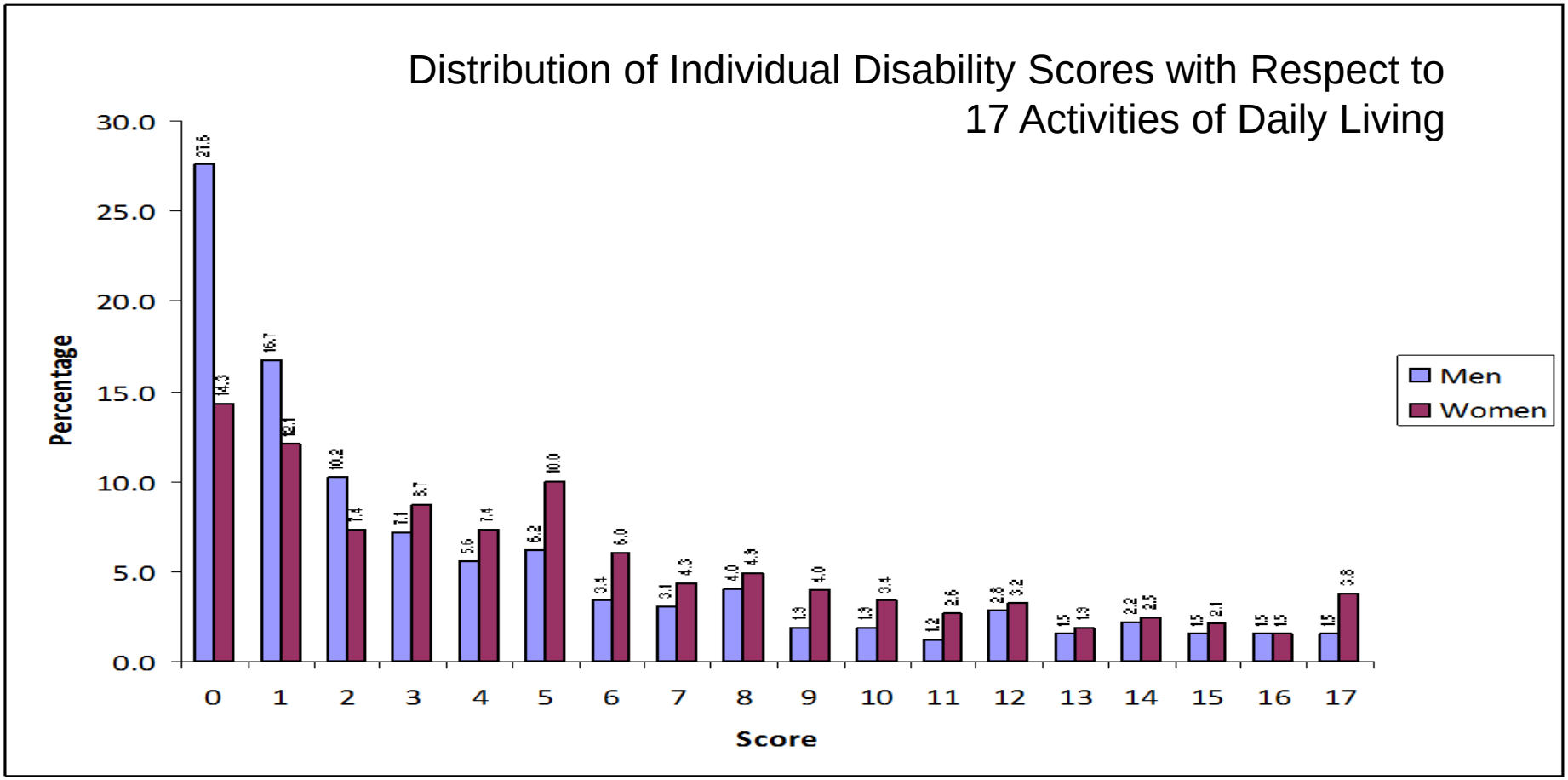


No one has perfect medical health at age 85.

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

Extreme Diversity in Capability/Disability at Advanced Old Age



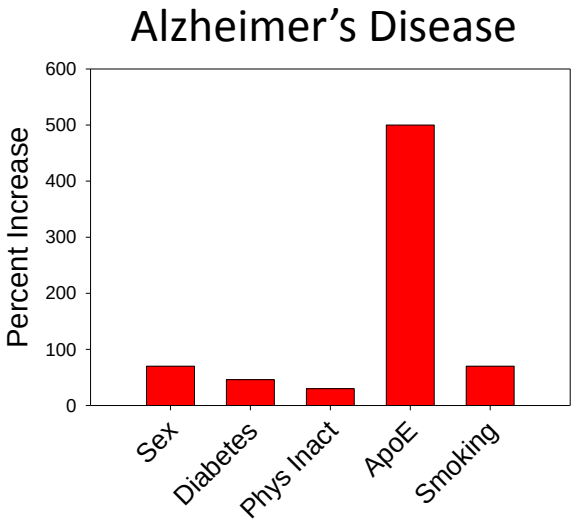
A quarter of men and a sixth of women have no important functional limitation at age 85.

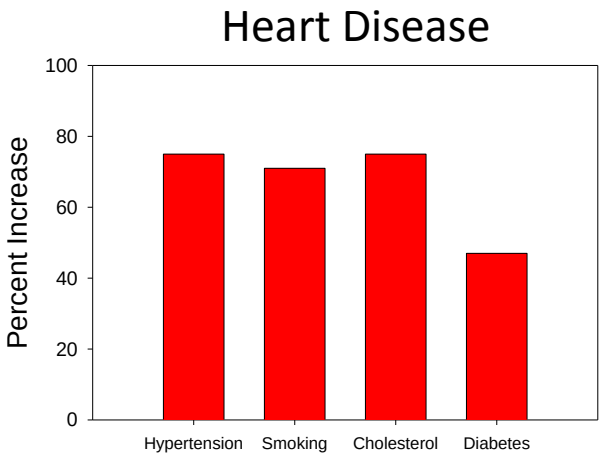
Collerton et al *British Medical Journal* 2009

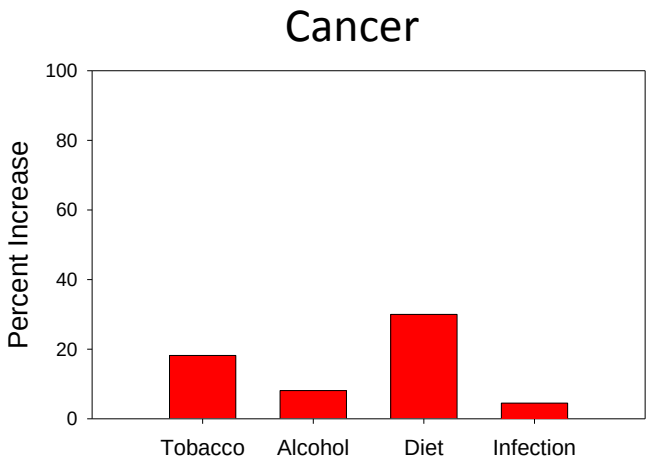
First things first

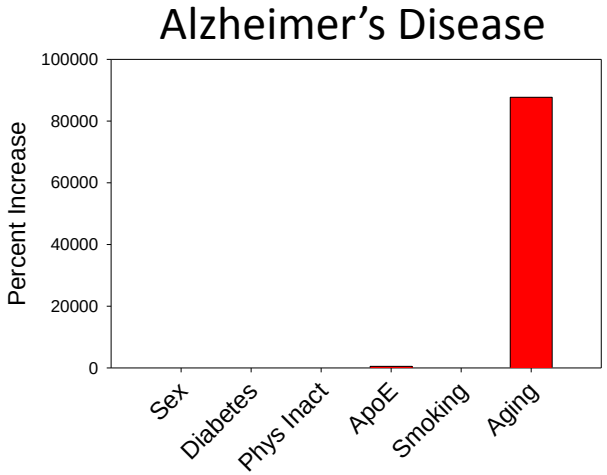
- Do we know why ageing occurs?
- Do we understand what determines longevity?
- What is already happening to human longevity?
- What accounts for the individuality of ageing?
- What does the latest research tell us about possible interventions?
- What are the key challenges for extending the human healthspan?

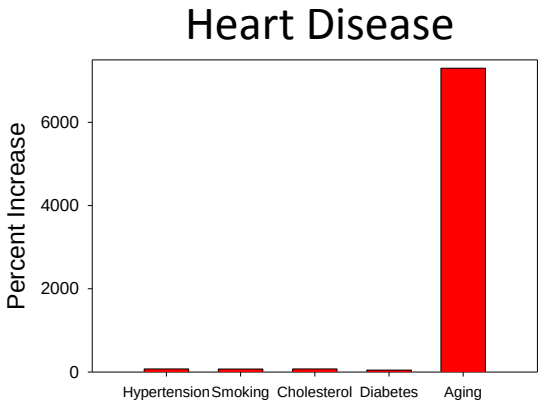
Risk Factors for Age-Related Diseases

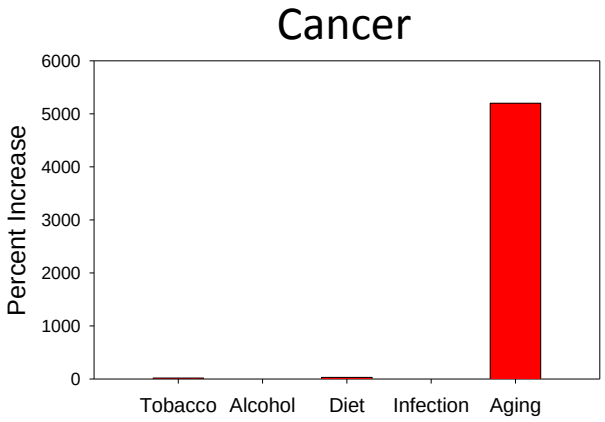








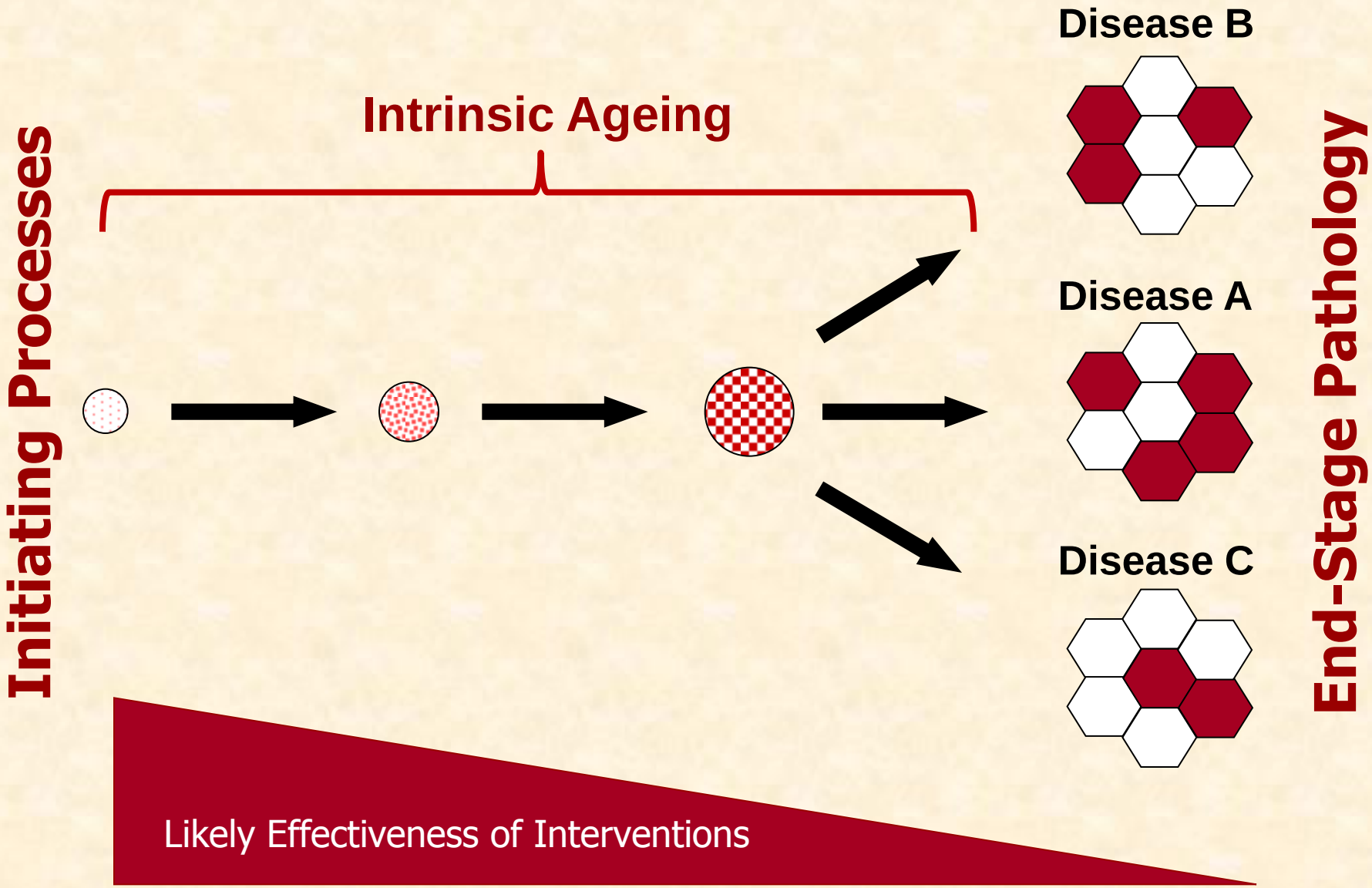




Source: Steve Austad

Intrinsic Ageing and Age-Related Disease

Accumulation of Molecular and Cellular Damage



Fundamental Mechanisms Shared by Intrinsic Ageing and Age-Related Diseases

- Molecular damage
  - DNA damage, protein aggregation, etc
- Cellular apoptosis
  - suicide by critically damaged cells
- Cellular senescence
  - permanent arrest of moderately damaged cells
- Stem cell deterioration
  - compromises tissue self-renewal
- Inflammation
  - chronic reaction to cell and molecular damage

The Search for Anti-Ageing Interventions

- Dietary restriction
- Fasting strategies
- Exercise
- Drugs (e.g. rapamycin, resveratrol, metformin)
- Transfer of young blood/plasma
- Targeted deletion of senescent cells (senolysis)

See, for example:
de Cabo et al *Cell* 2014
Baker et al *Nature* 2016
Kaiser *Science* 2016

First things first

- Do we know why ageing occurs?
- Do we understand what determines longevity?
- What is already happening to human longevity?
- What accounts for the individuality of ageing?
- What does the latest research tell us about possible interventions?
- What are the key challenges for extending the human healthspan?

Prolonging Healthspan – Key Challenges

- Timescales
  - May be decades between intervention and outcome
- Trials and regulation
  - Effective interventions likely to require treating ‘healthy’ people
- Metrics – biomarkers and complexity
  - Measuring true biological age remains elusive
- Trade-offs, constraints, and side-effects
  - Ageing strongly influenced by intrinsic physiological trade-offs
- The ‘species problem’
  - What works in short-lived animals may not work in humans
- Patchiness of baseline data
  - Health data much sparser than for lifespan

Biomarker Domains in Newcastle 85+ Study

Anthropometry, blood pressure and physical function

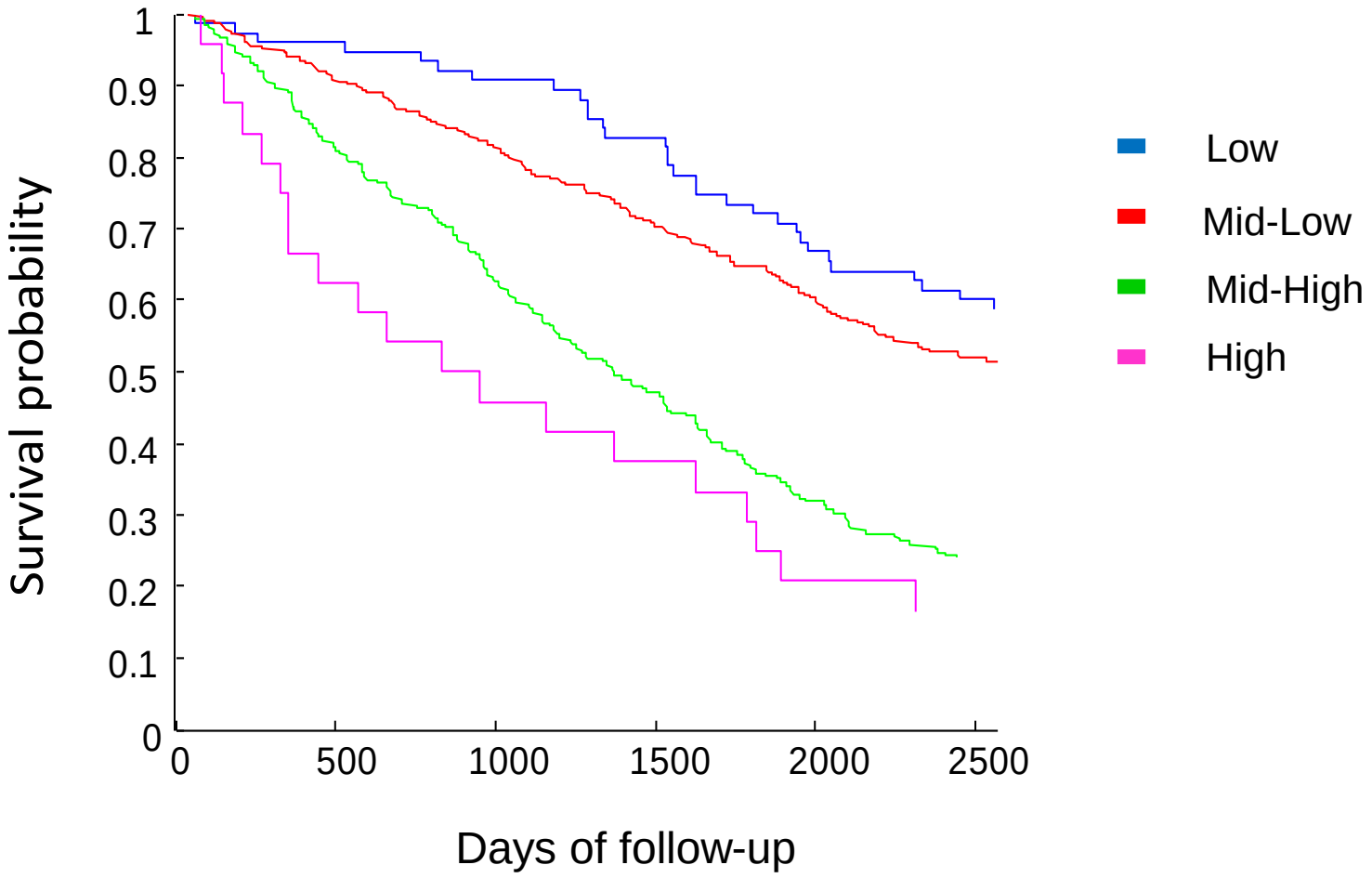
- Weight, body fat percentage, body fat mass, fat free mass and total body water
- Diastolic and systolic blood pressures
- Right and left hand-grip strength
- Timed Up-and-Go (TUG) test; 7-day continuous activity monitoring
- Respiratory function

Blood-based biomarkers

- Haematology and biochemistry:
- Nutritional markers
- Inflammatory response
- Lymphocyte subpopulations
- Telomere length
- DNA Damage and Repair
- Plasma isoprostanes

Martin-Ruiz et al *Mech Ageing Dev* 2011

Biomarker-based Frailty Index Predicts 7-year Mortality



Mitnitski et al *BMC Medicine* 2015

Other Relevant Studies

Waaijer et al. *Exp Gerontol* 2016

178 participants in Leiden Longevity Study (age range 42-82). Molecular measures more weakly associated with age than functional measures.

Gunn et al. *J Gerontol Med Sci* 2015

187 Danish twin pairs aged 70+. Perceived age (based on photographs) associated with survival over 7+ years.

Belsky et al. *Proc Natl Acad Sci USA* 2015

Dunedin birth cohort (1037 individuals followed birth to age 38). Measured function of multiple organ systems (pulmonary, periodontal, cardiovascular, renal, hepatic, immune). Claims to assess 'biological ageing' before onset of age-related diseases.

Sood et al. *Genome Biology* 2015

Samples from multiple cohorts used to create "healthy ageing RNA classifier" associated with cognitive health status.

Sayer & Kirkwood *Lancet* 2015

Hand grip strength as biomarker of ageing.

So although we cannot measure biological age precisely, we can see that there are many biological factors that relate to increasing frailty and mortality.

How can we relate this to the evident malleability of the ageing process?

As life expectancy increases:
- do biomarkers show changes later?
- do diseases develop later?
- do we see compression of morbidity?

Prolonging Healthspan – Key Challenges

- Timescales
  - May be decades between intervention and outcome
- Trials and regulation
  - Effective interventions likely to require treating ‘healthy’ people
- Metrics – biomarkers and complexity
  - Measuring true biological age remains elusive
- Trade-offs, constraints, and side-effects
  - Ageing strongly influenced by intrinsic physiological trade-offs
- The ‘species problem’
  - What works in short-lived animals may not work in humans
- Patchiness of baseline data
  - Health data much sparser than for lifespan

How has the risk of dementia changed over 20 years?

Cognitive Function and Ageing Study (CFAS).

Three geographical regions of England (including Newcastle).

CFAS I – 1989-1994 (7635 people aged 65 and over)
CFAS II – 2008-2011 (7796 people aged 65 and over)

- Using CFAS I age and sex specific prevalence estimates, 8.3% of the CFAS II study population would be expected to have dementia.

- However, the actual prevalence of dementia in CFAS II was just 6.5%.

Matthews et al *Lancet* 2013

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?

Thank you

Centre for Integrated Systems Biology of Ageing and Nutrition

Newcastle 85+ Study team

Institute for Ageing and Health (now NUIA)