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Why and How Are Living Longer?

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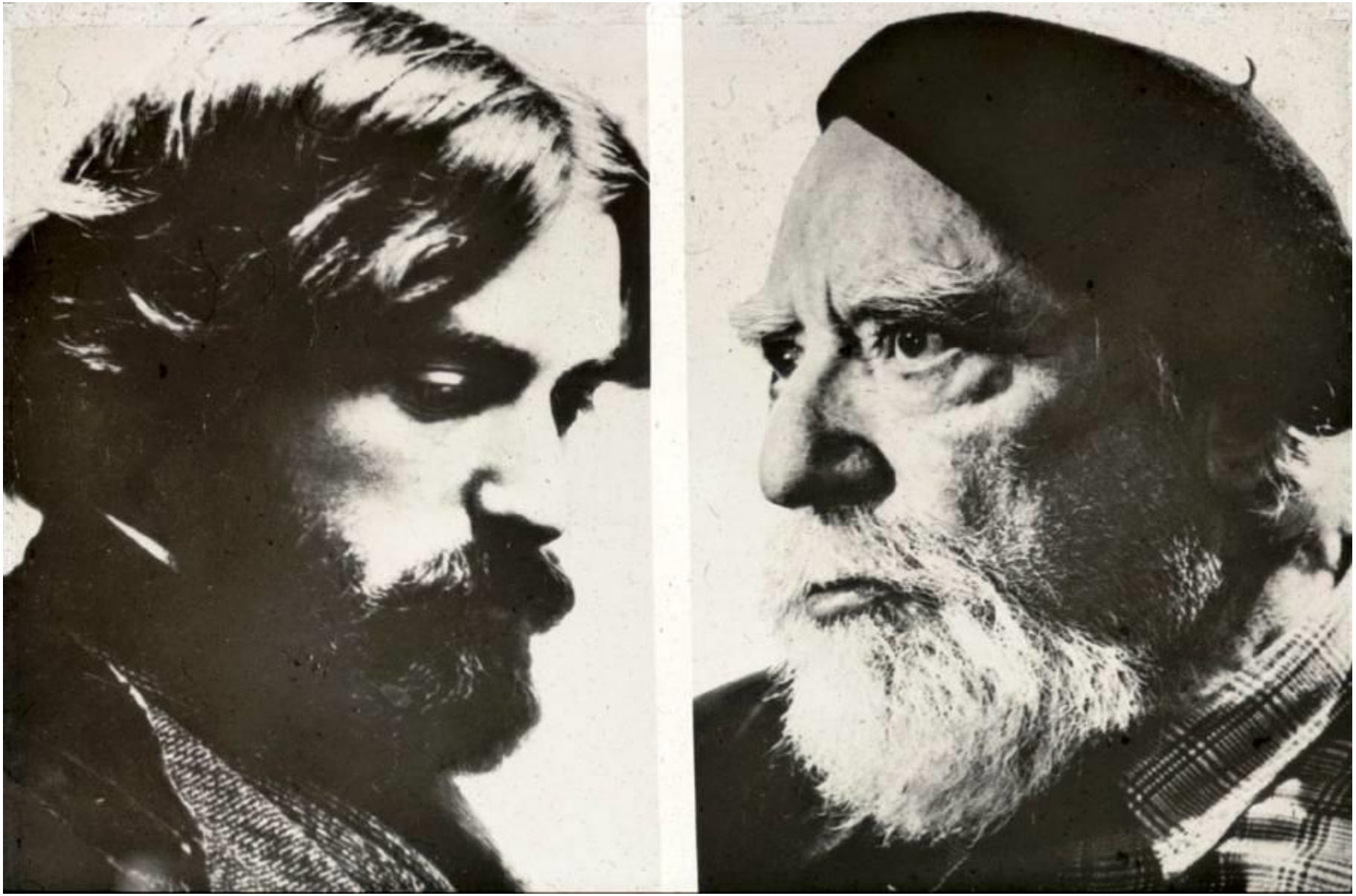
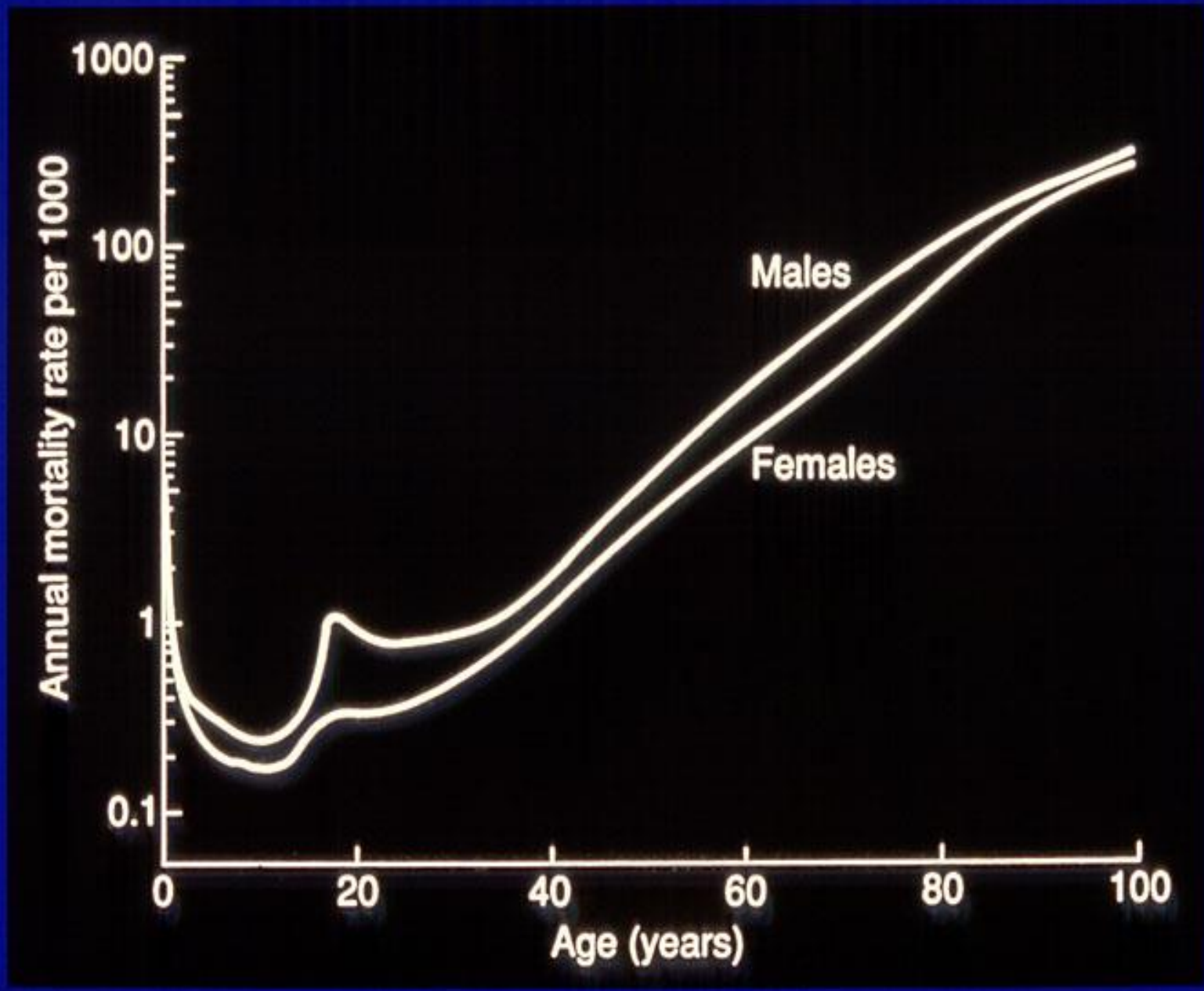


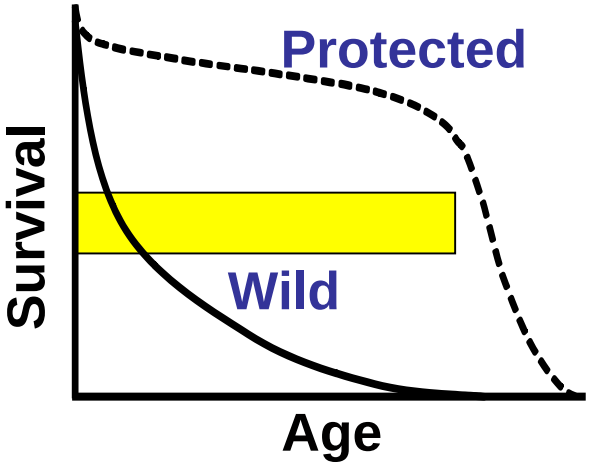
What happened? Why??

Age and Sex Specific Mortality Rates for Humans



Why Ageing Occurs

- Contrary to widely held belief, the body is NOT programmed to age and die.



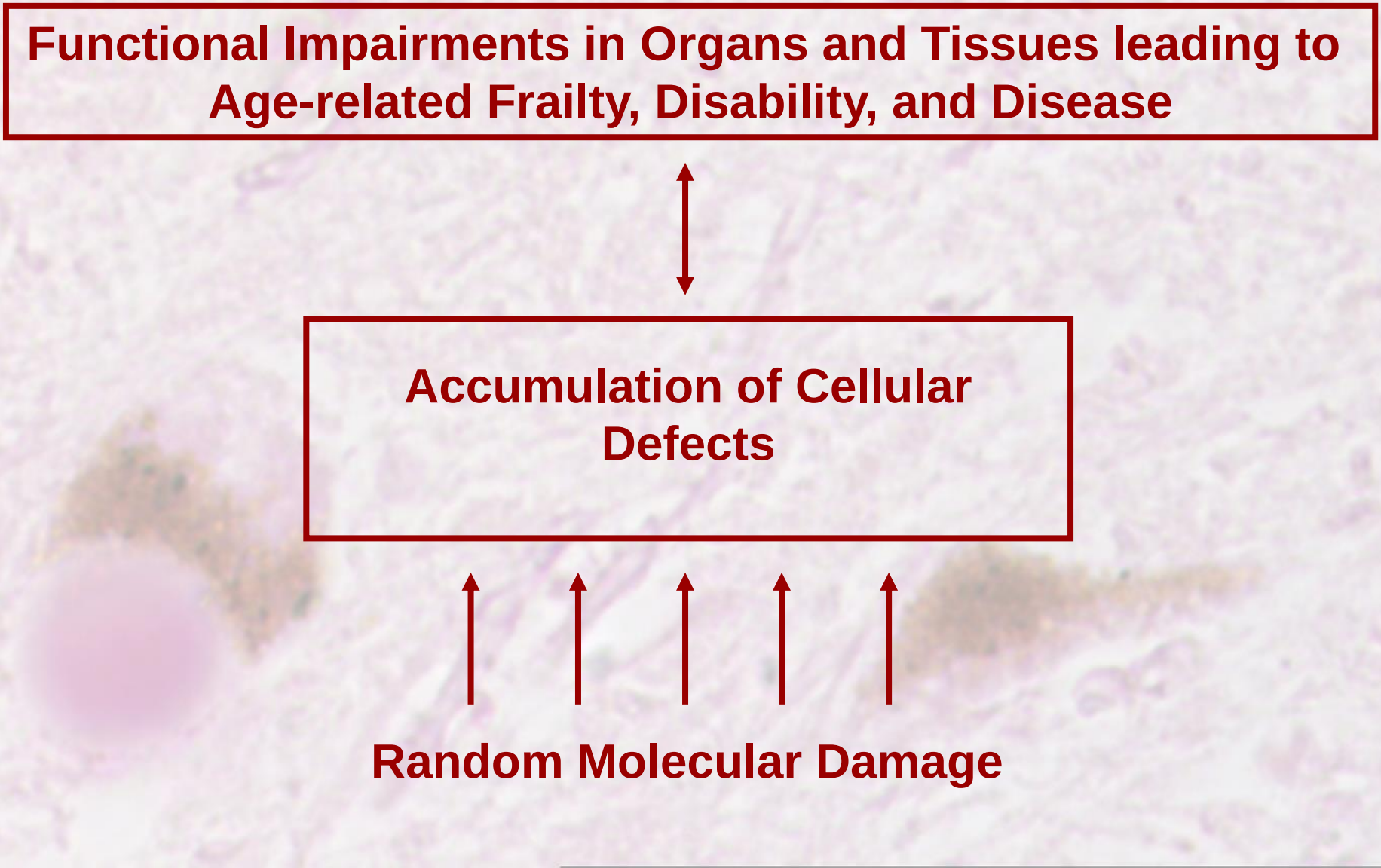
- Indeed, the body is programmed for survival. However, there was no evolutionary pressure to invest in a body that might live forever.

Disposable Soma

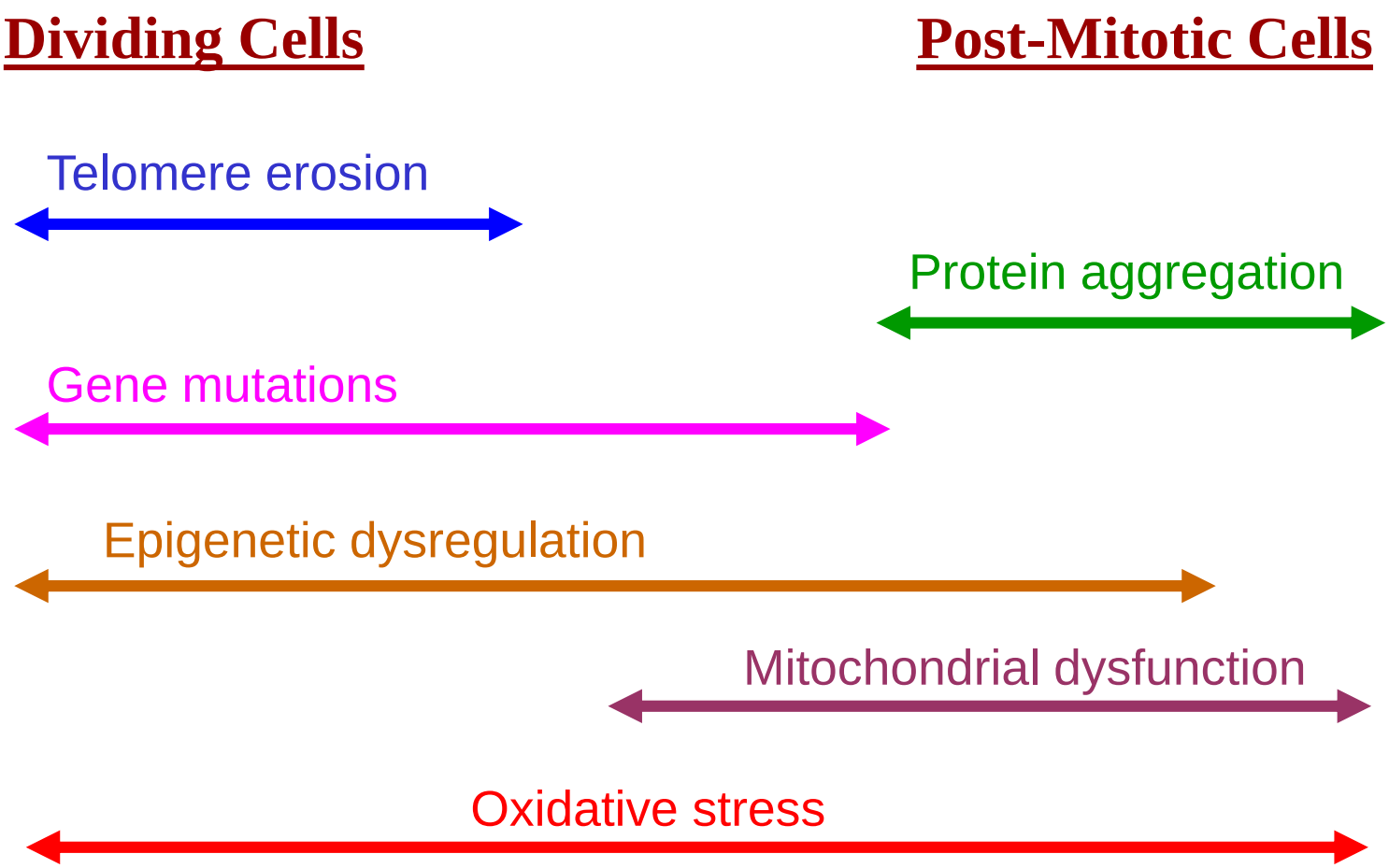
Kirkwood *Nature* 1977

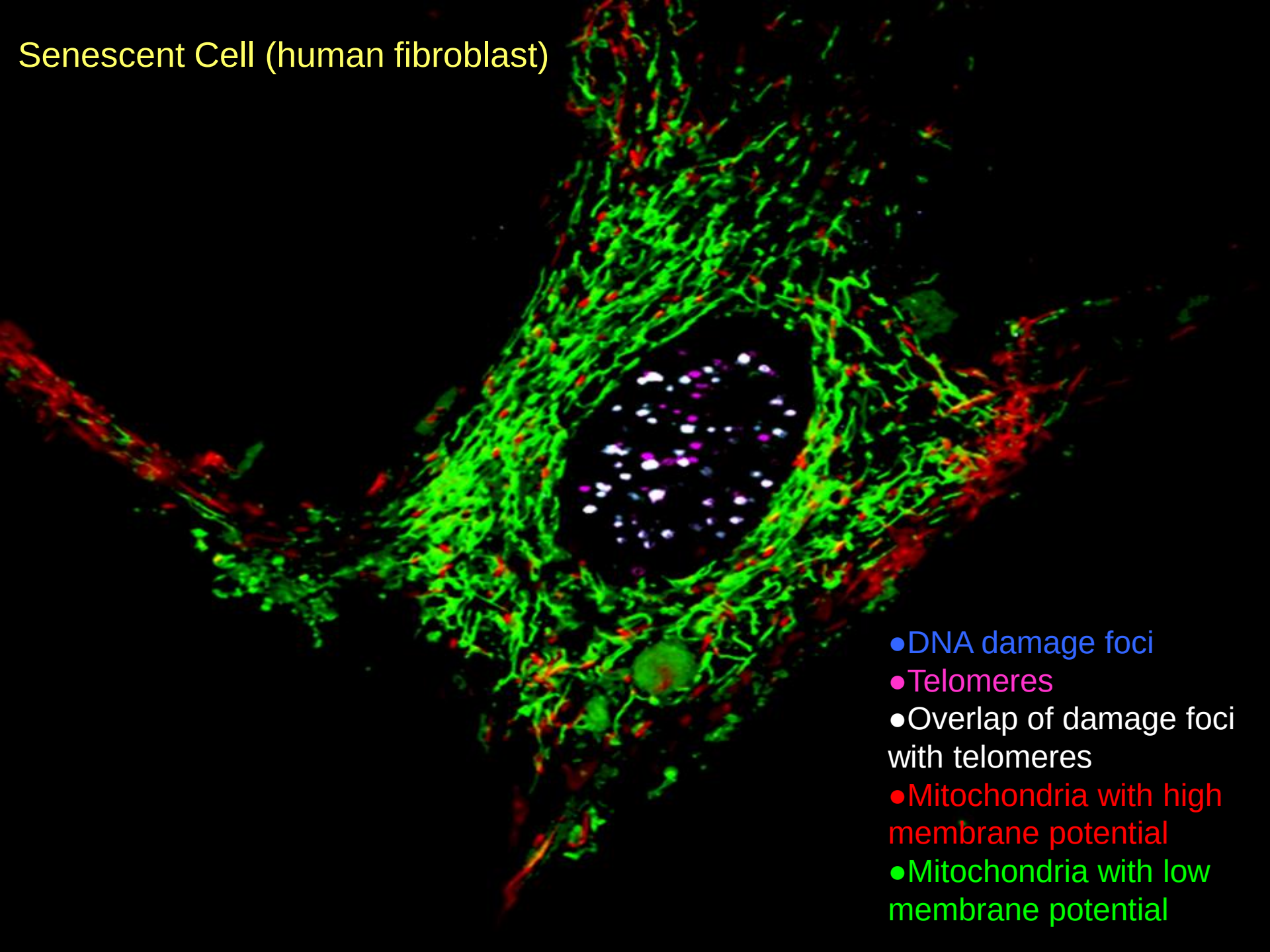
- Ageing is caused by the accumulation of damage.

The Ageing Process



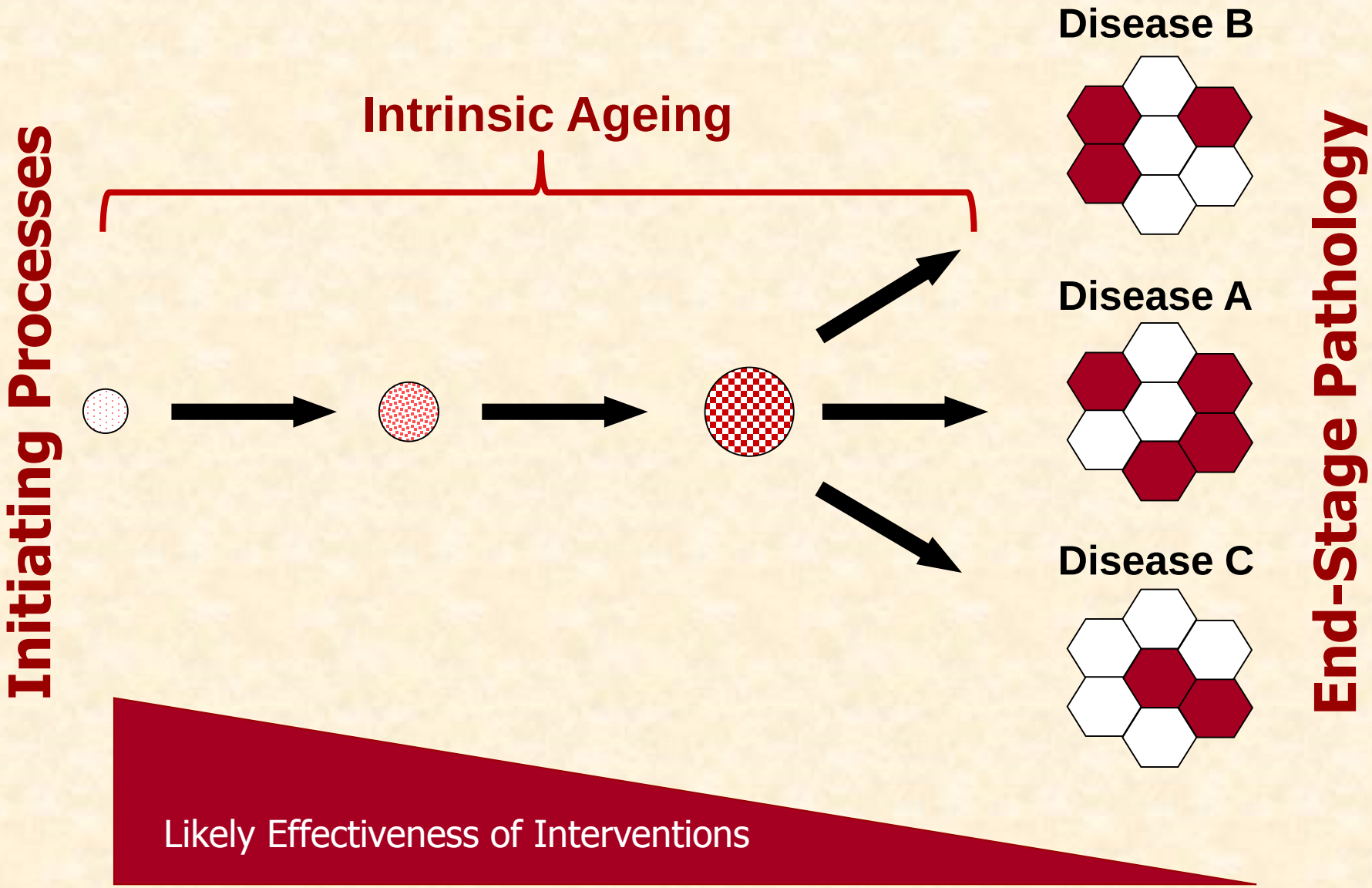
Molecular Mechanisms of Intrinsic Ageing




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

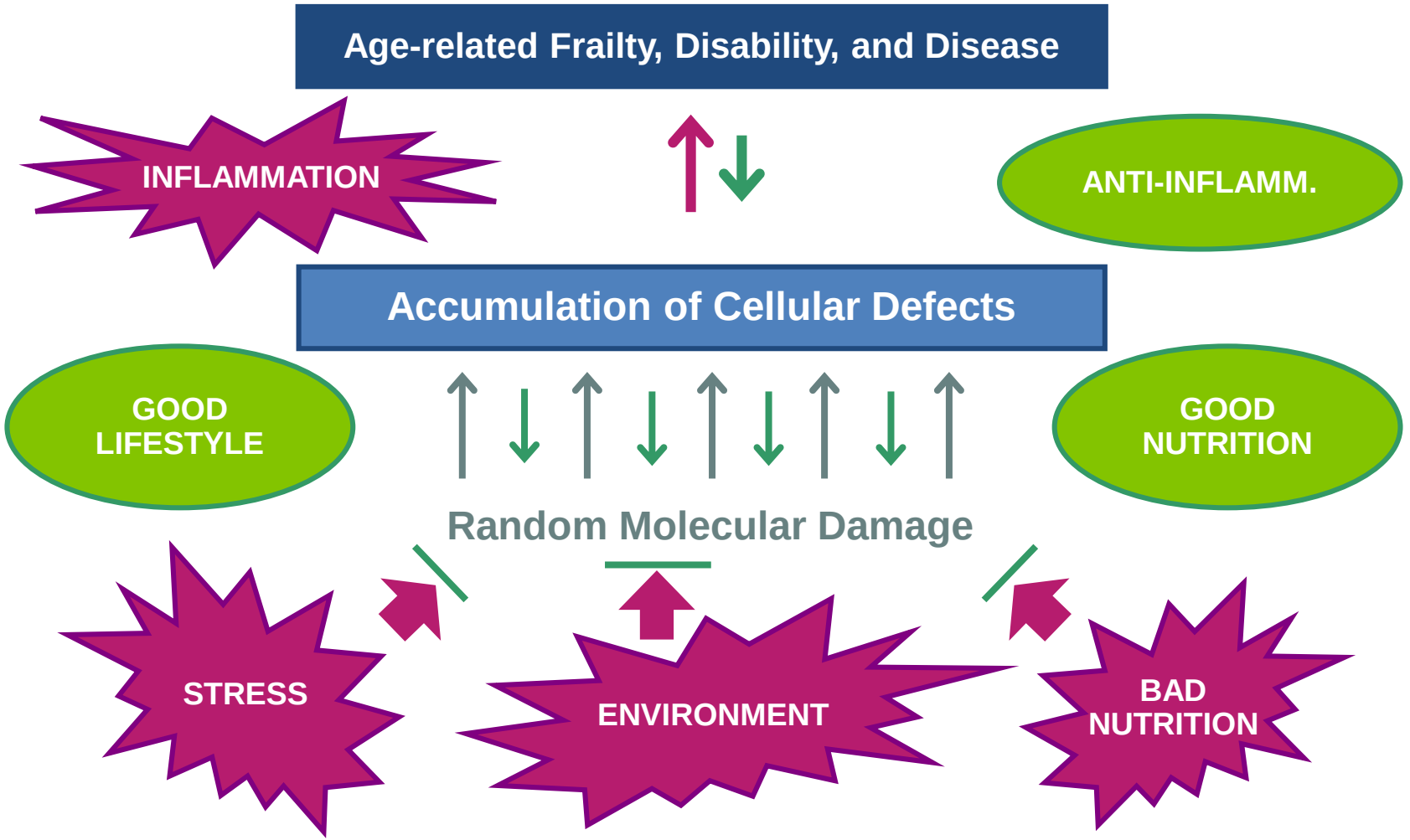
Intrinsic Ageing and Age-Related Disease

Accumulation of Molecular and Cellular Damage



HUMAN AGEING AND ITS MALLEABILITY

Kirkwood *Cell* 2005



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

Factors Influencing Health Trajectories in Old Age

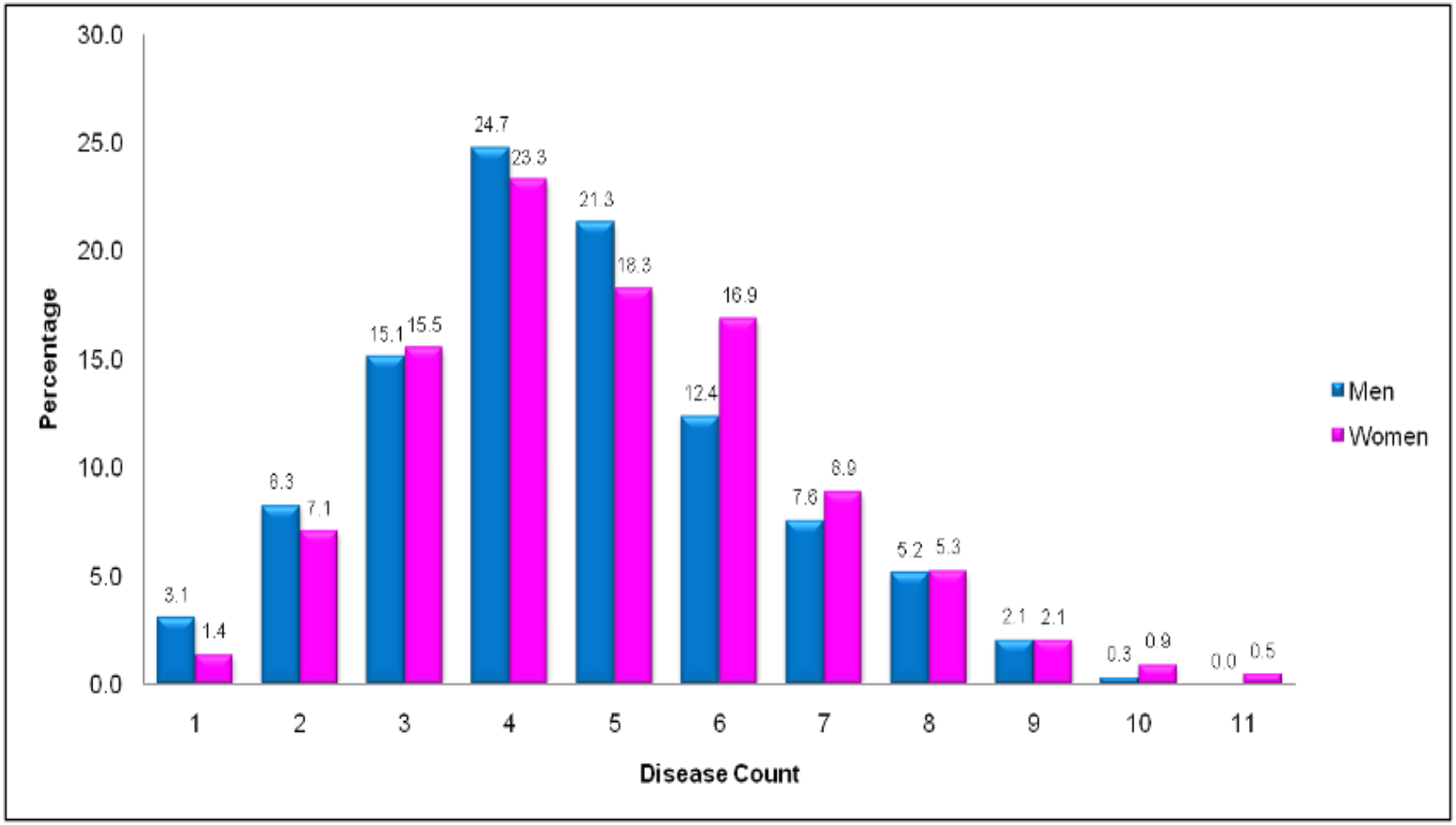
Newcastle 85+ Study; prospective study in 1000+ individuals born in 1921

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

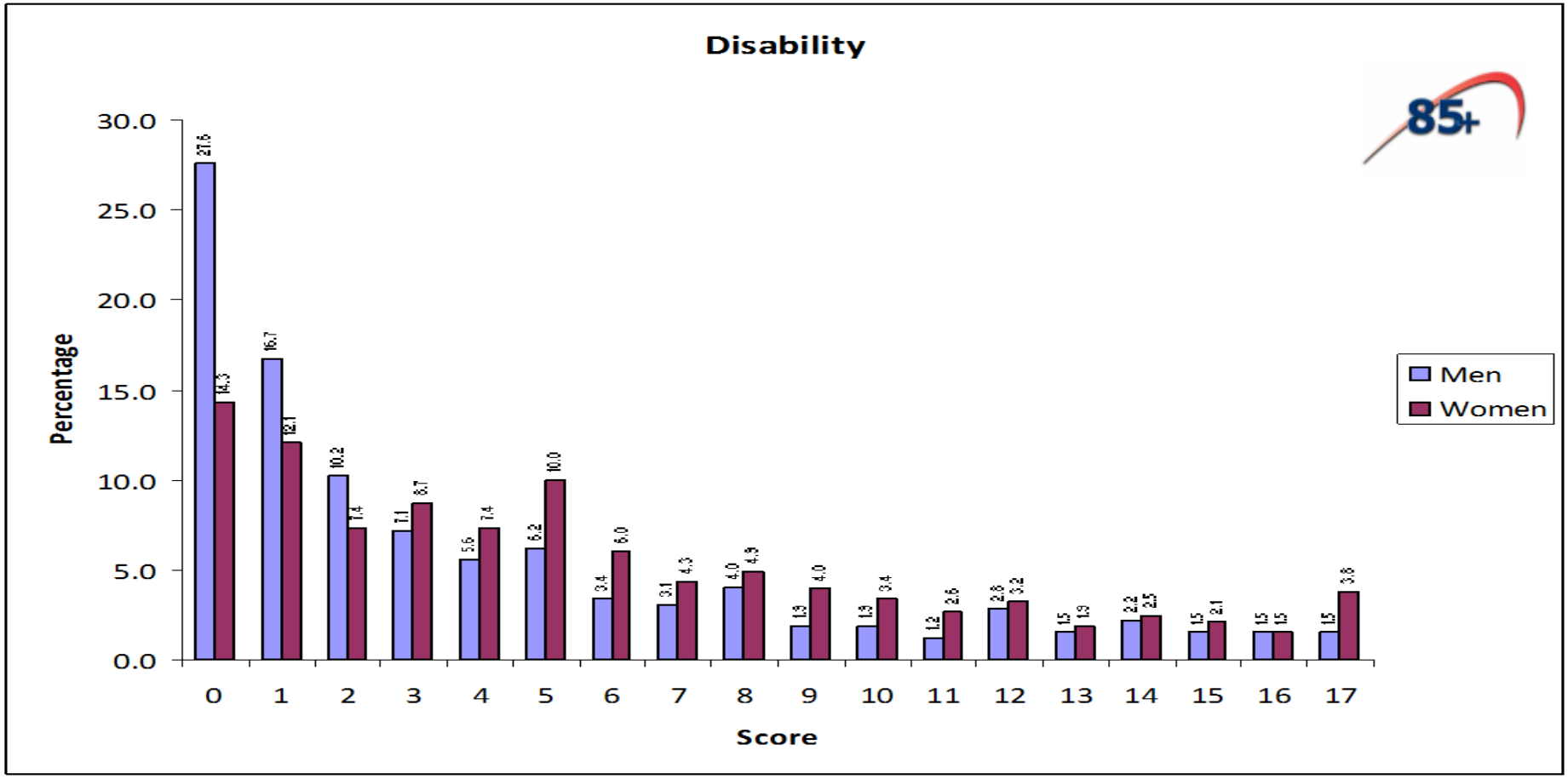


No one has perfect medical health at age 85.

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

A “Holy Grail” of Ageing Science

Can we relate health status to intrinsic markers of biological age?

Success would enable:

- Pensions and life insurance risk assessment.
- Early evaluation of interventions to improve healthy life expectancy.
- Personalised monitoring of age-related health trajectories.

A novel multi-tissue RNA diagnostic of healthy ageing relates to cognitive health status

Sood et al *Genome Biology* 2015

"We identify a novel and statistically robust multi-tissue RNA signature of human healthy ageing that can act as a diagnostic of future health, using only a peripheral blood sample. This RNA signature has great potential to assist research aimed at finding treatments for and/or management of AD and other ageing-related conditions."

Biomarker Domains in Newcastle 85+ Study

Anthropometry, blood pressure and physical function

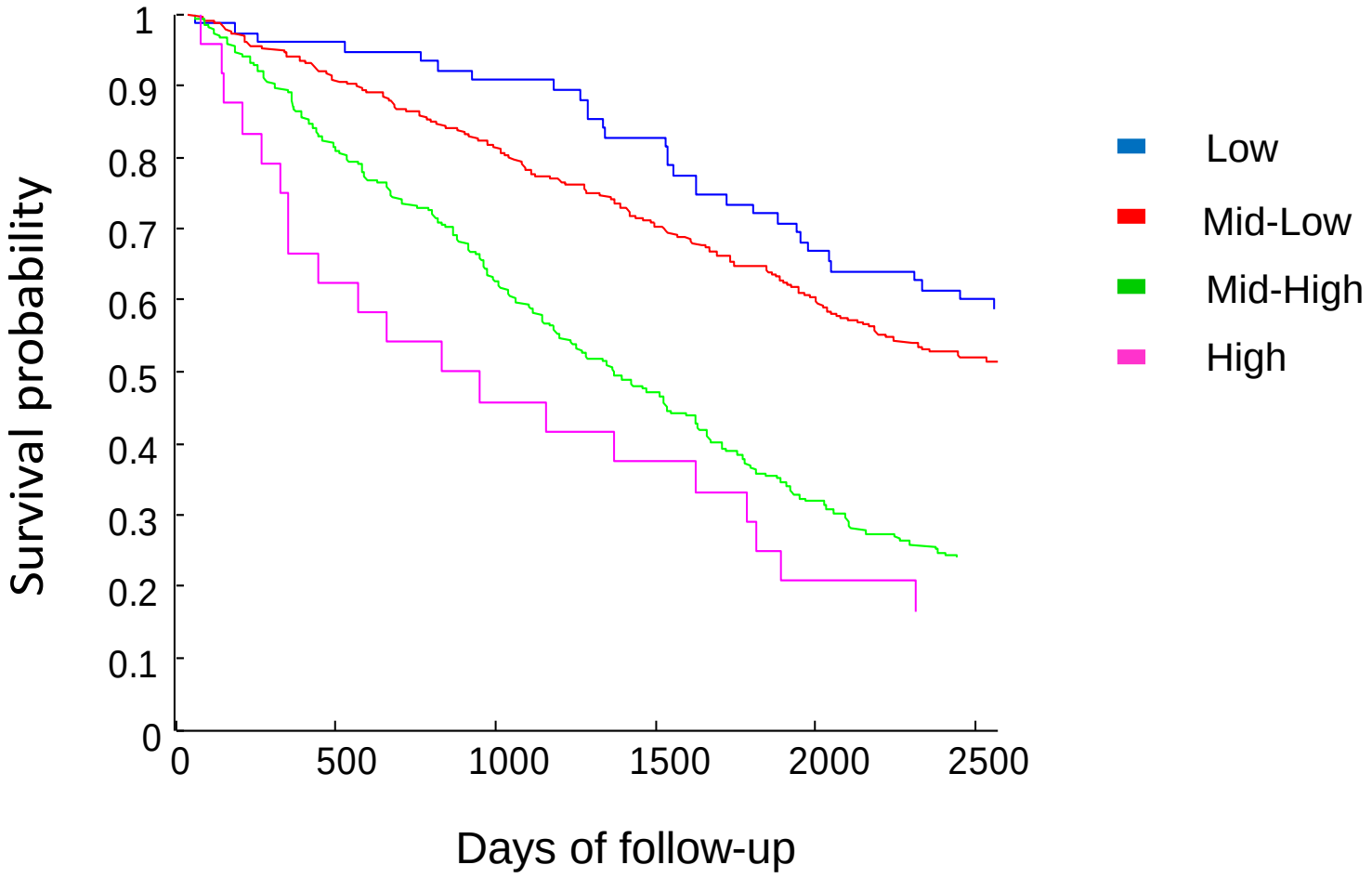
- Weight, body fat percentage, body fat mass, fat free mass and total body water
- Diastolic and systolic blood pressures
- Right and left hand-grip strength
- Timed Up-and-Go (TUG) test; 7-day continuous activity monitoring
- Respiratory function

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

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?

Two-decade comparison of prevalence of dementia

Matthews et al *Lancet* 2013

Cognitive Function and Ageing Study (CFAS).
Three geographical regions of England.

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

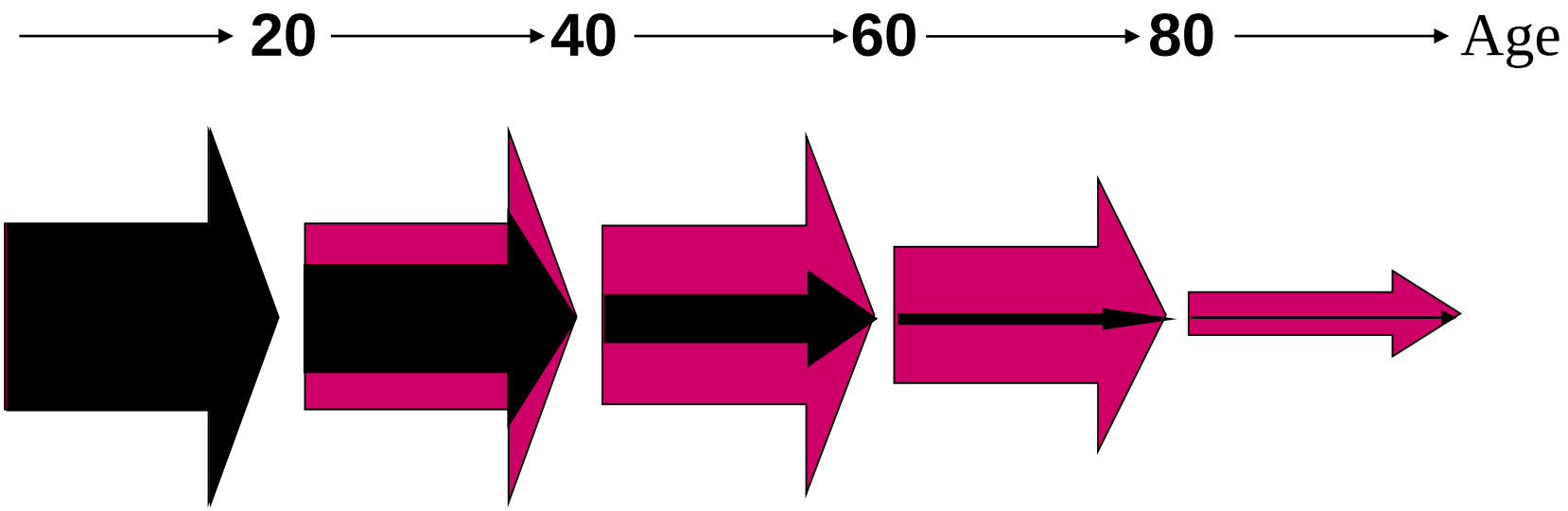
- Using CFAS I age and sex specific prevalence estimates, 8.3% of the CFAS II study population would be expected to have dementia.

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

Getting to Grips with Changes in Health Expectancy

- Despite the importance of health expectancy in policy, monitoring trends both within and between countries is problematic.
- Lack of harmonisation of health measures remain the major limitation, together with differences in survey design and calculation methods.
- The Global Burden of Disease programme has to some extent overcome these deficiencies using complex modelling techniques to estimate healthy life expectancy for 187 countries worldwide (Salomon et al. *Lancet* 2012).
- Latest data suggest an expansion of ill-health and disability in the UK, France, Netherlands, Japan and the USA but not in Belgium, Sweden or Switzerland (where LE gains appear smaller).

Now Living – Formerly Dead



Differences in survival using death rates from Registrar-General of England & Wales for 1900 (black) and 2000 (pink)

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?

Barriers to Achieving the Necessary Progress

- Fatalism
- Prejudice (explicit and implicit)
- Reluctance to address complexity
- Narrowness of vision
- Short-termism
- Funding constraints

Thank you

Centre for Integrated Systems Biology of Ageing and Nutrition

Newcastle 85+ Study team

Institute for Ageing and Health (now NUIA)