Evolutionary Foundation of Ageing and Longevity

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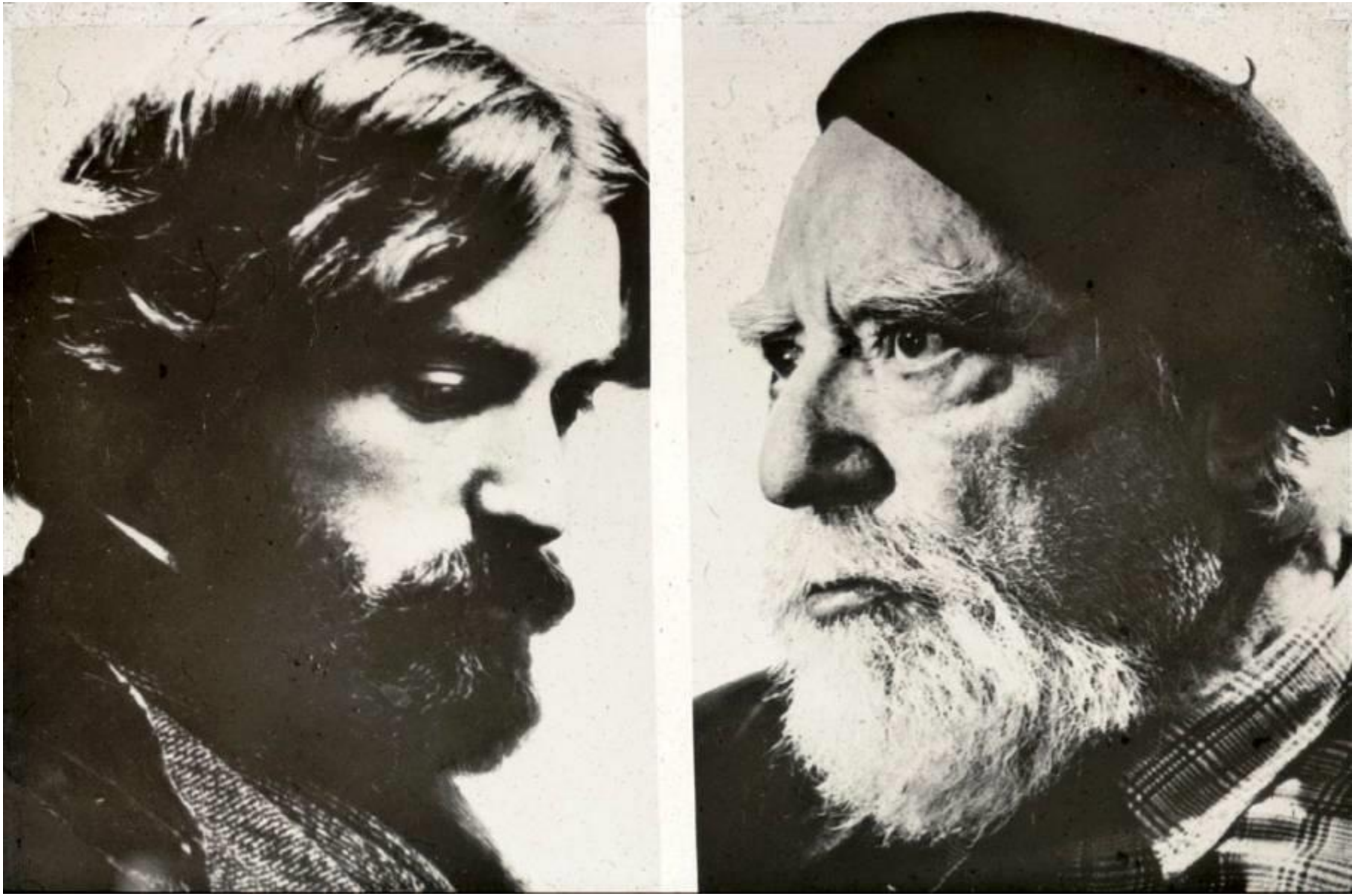
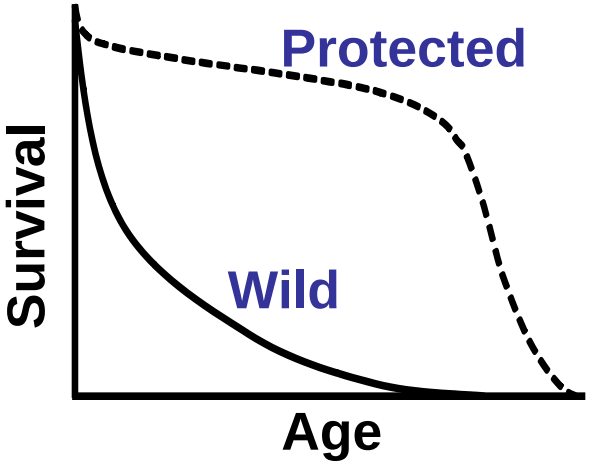


What happened? Why??

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 aging, if it existed, would be ‘unstable’.
- No immortal mutants are observed.



Kirkwood & Melov *Current Biology* 2011

But What About …

- Pacific salmon?
- Menopause?

Are these not examples of programmed ageing?

More on this later…

So Why Does Ageing Occur?

DECLINING FORCE OF NATURAL SELECTION

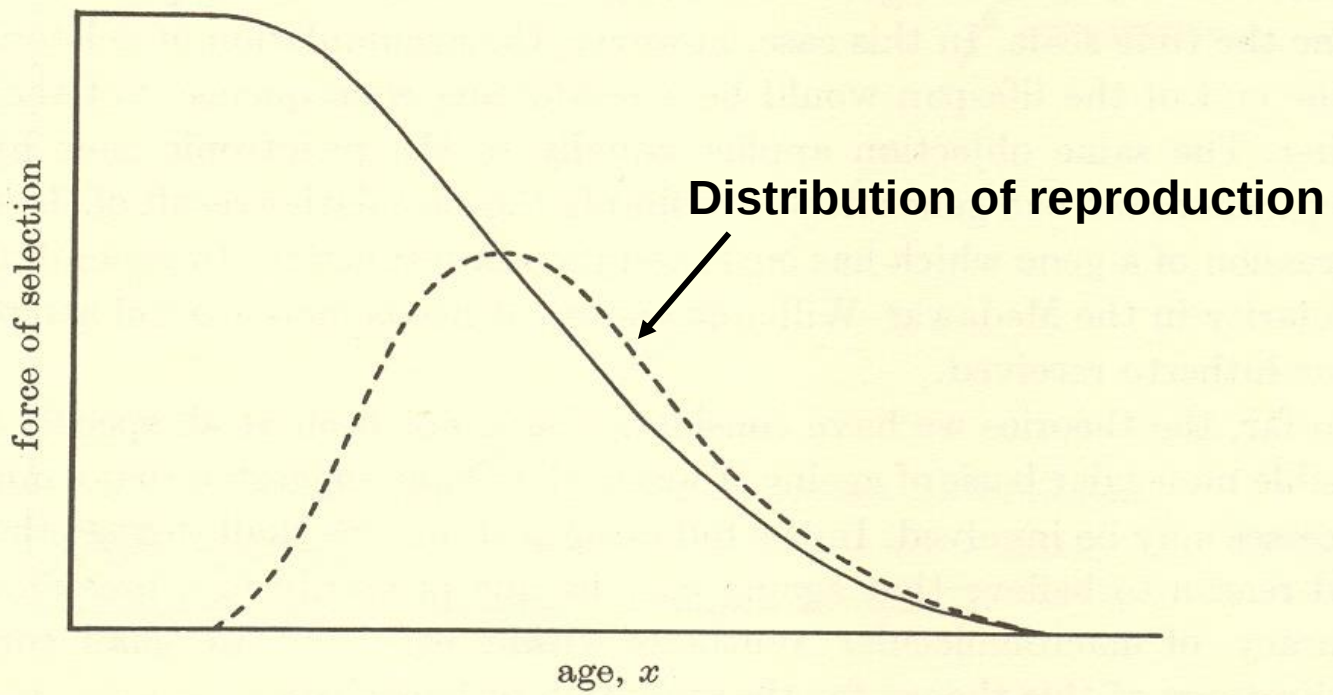
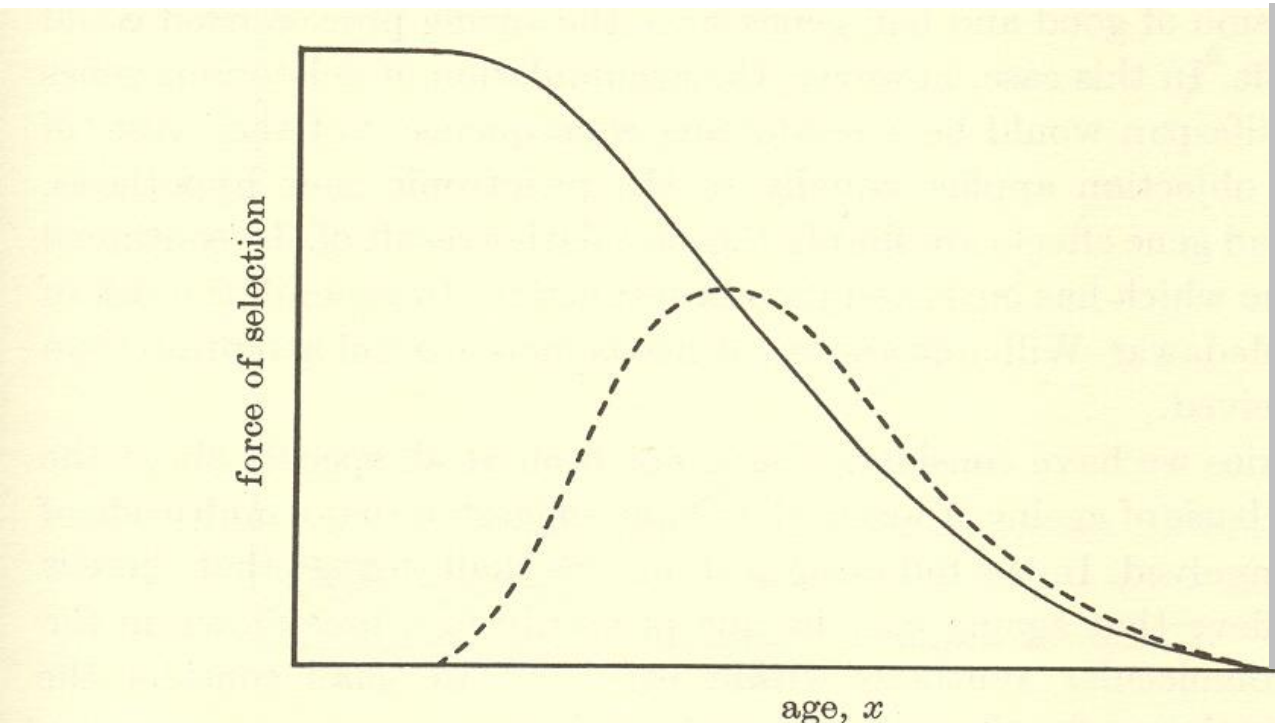


FIGURE 3. The broken curve represents the quantity $p_x = l_x b_x$ (see text) for a typical population; this equals the expected rate of reproduction at age x for a newborn individual, taking account of the possibility of prior mortality. The area under the broken curve is the total expectation of reproduction. The solid curve, representing the remaining fraction of the total expectation of reproduction at any age, is a measure of the force of natural selection acting at that age.

Kirkwood & Holliday *Proc R Soc* 1979

SELECTION ON GENES WITH AGE-SPECIFIC EFFECTS ON FITNESS



Selection Shadow

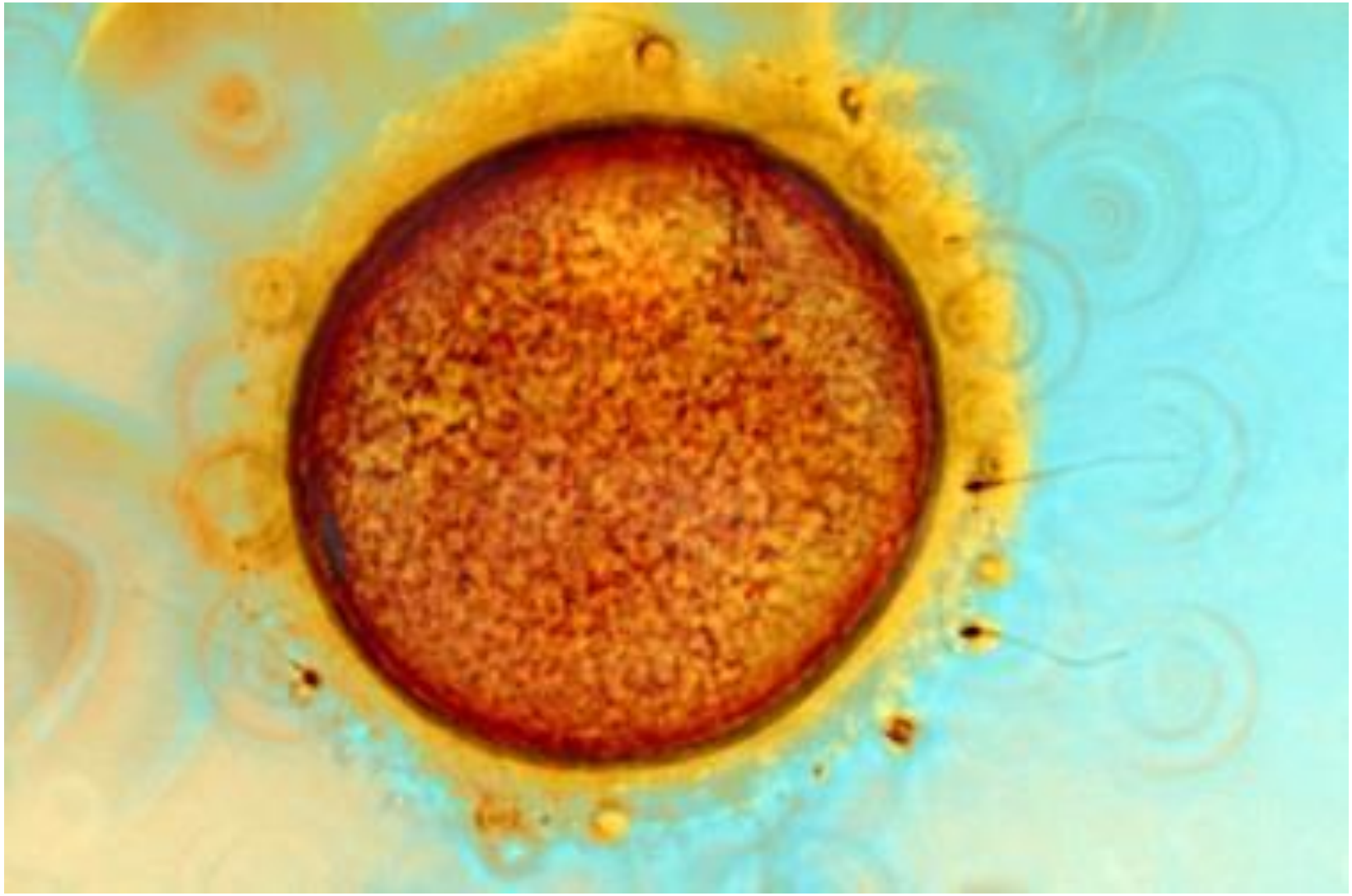
(late-acting deleterious mutations may accumulate).

Medawar 1952

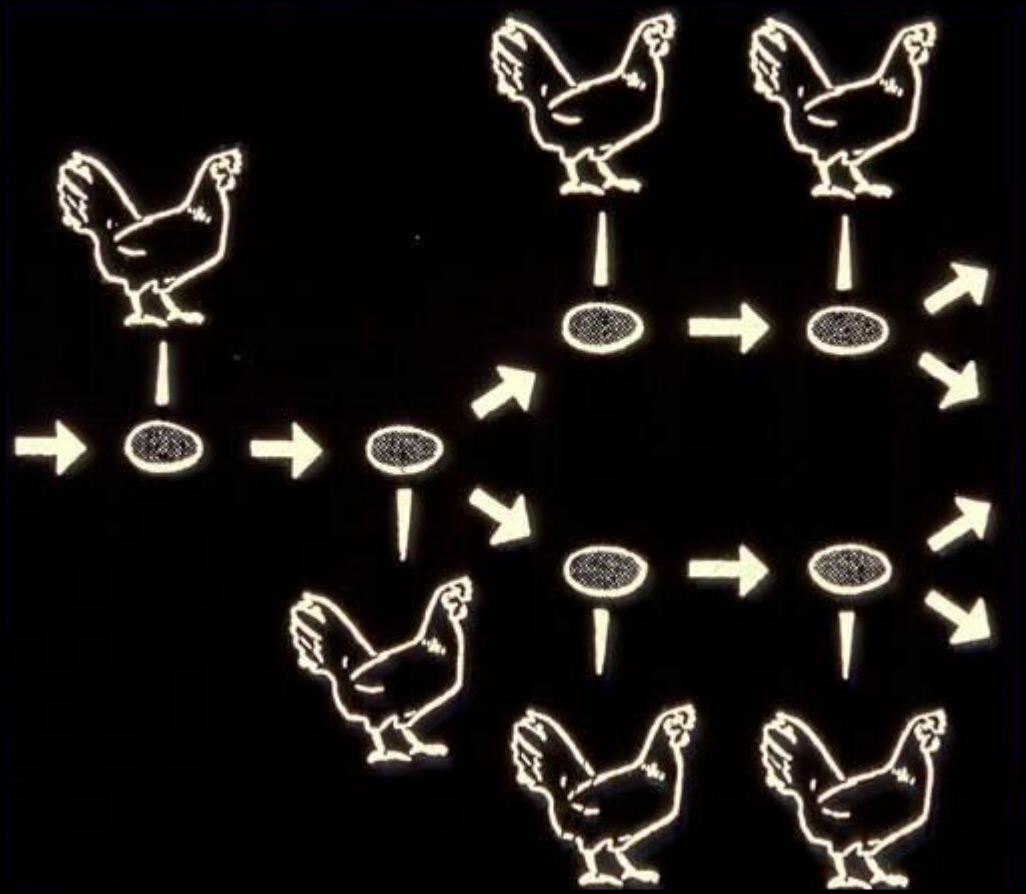
For genes with **Age Pleiotropy**, selection will tend to advance good and postpone bad effects.

Williams 1957

Life – a Sexually Transmitted Condition with an Invariably Fatal Outcome



Immortal Germ-Line – Mortal Soma

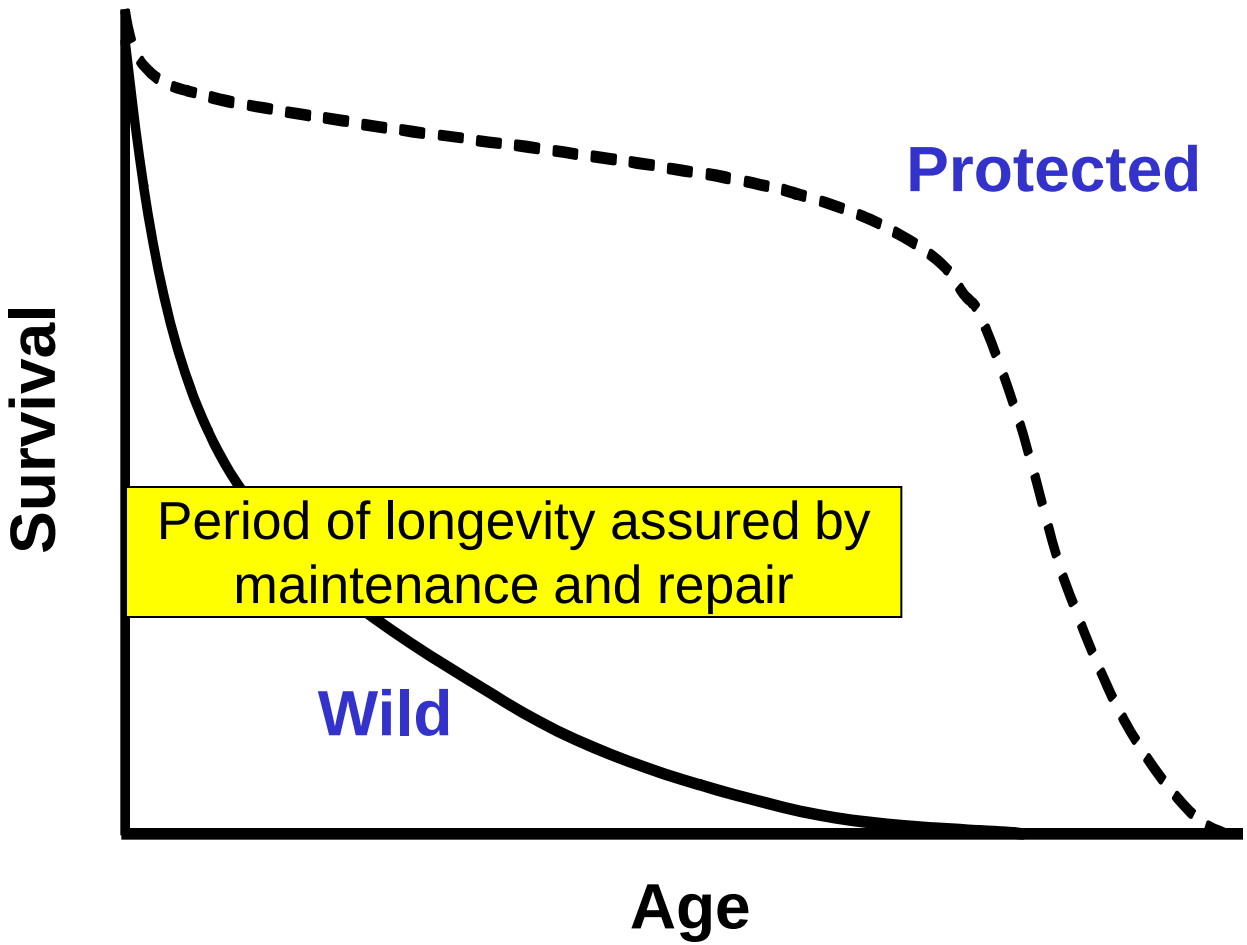


August Weismann

The Central Role of Metabolism – Resource Allocation and Evolutionary Fitness

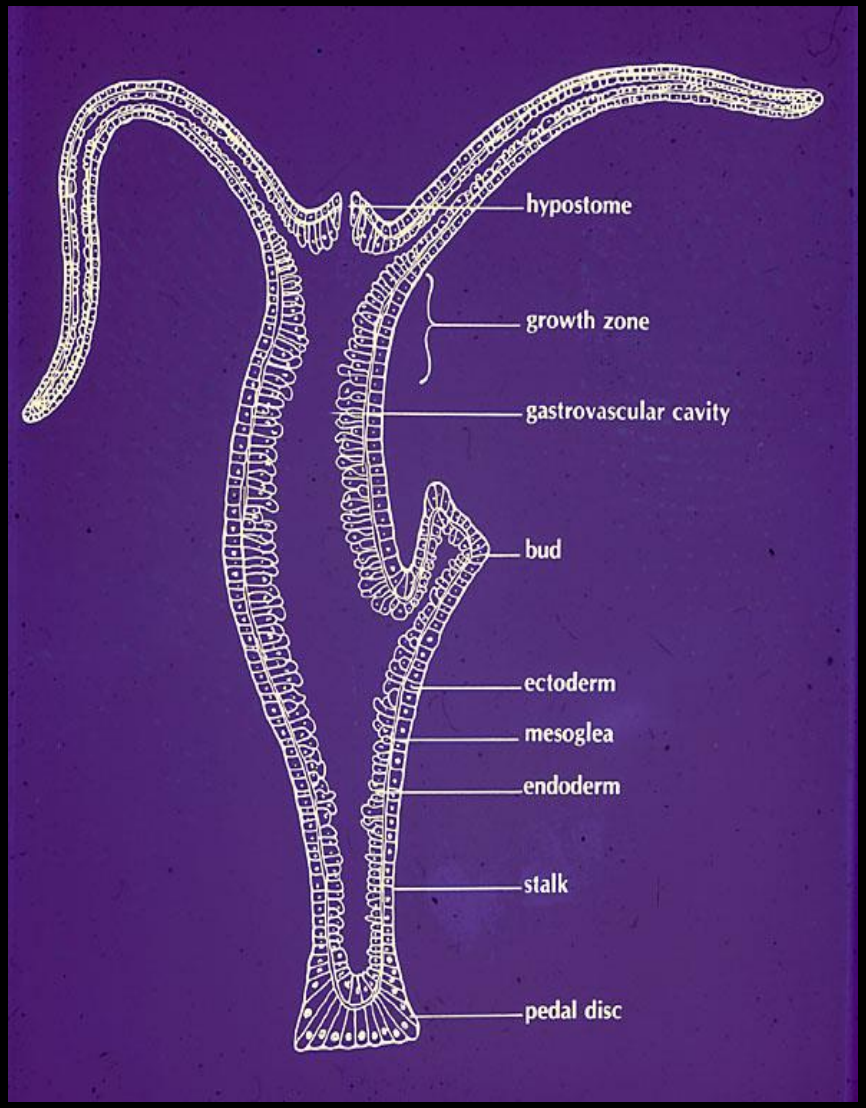
Kirkwood (1981) in *Physiological Ecology: An Evolutionary Approach to Resource Use* (eds Townsend & Calow)

DISPOSABLE SOMA THEORY



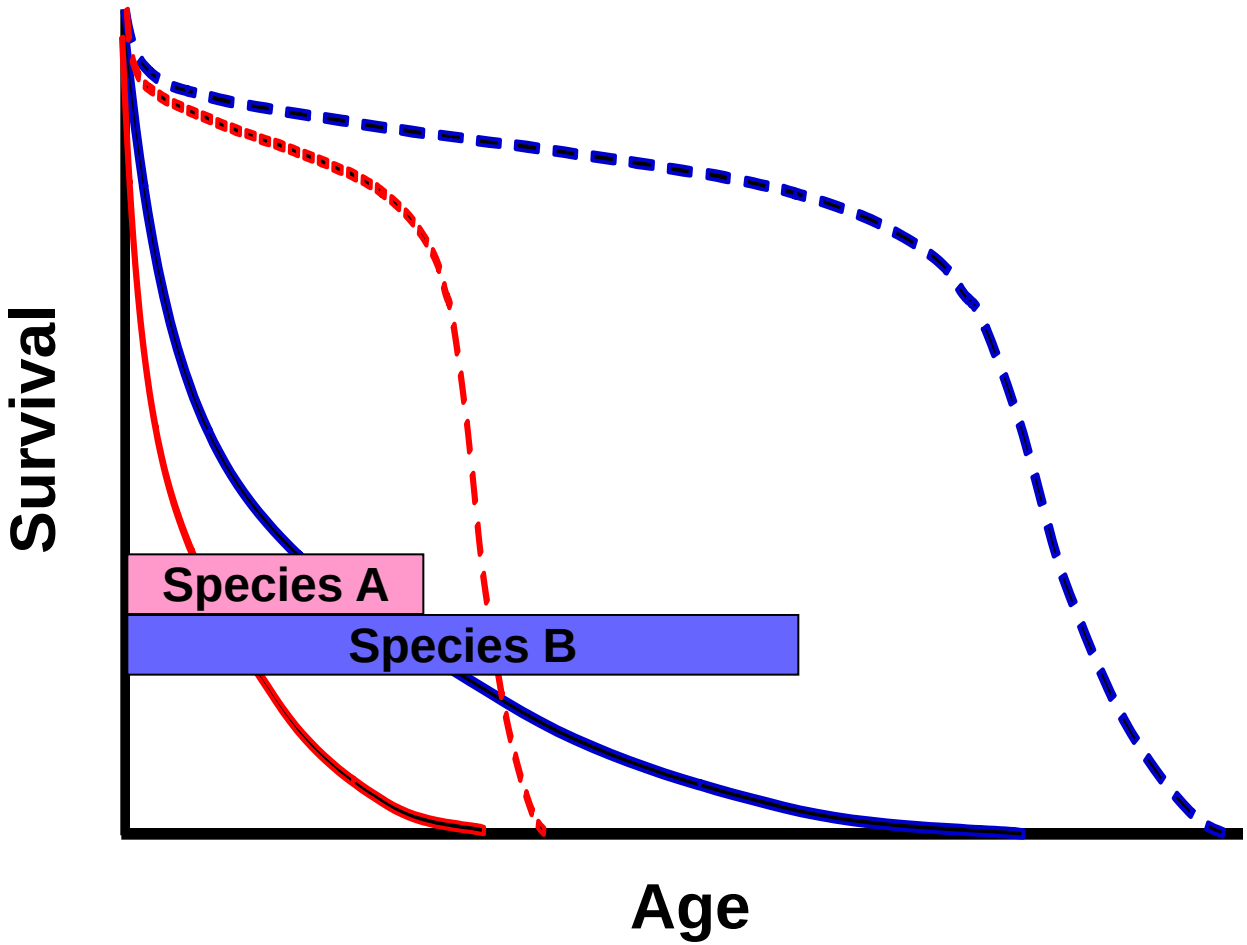
Kirkwood *Nature* 1977

An Exception Which Proves The Rule - ‘Immortal’ Hydra



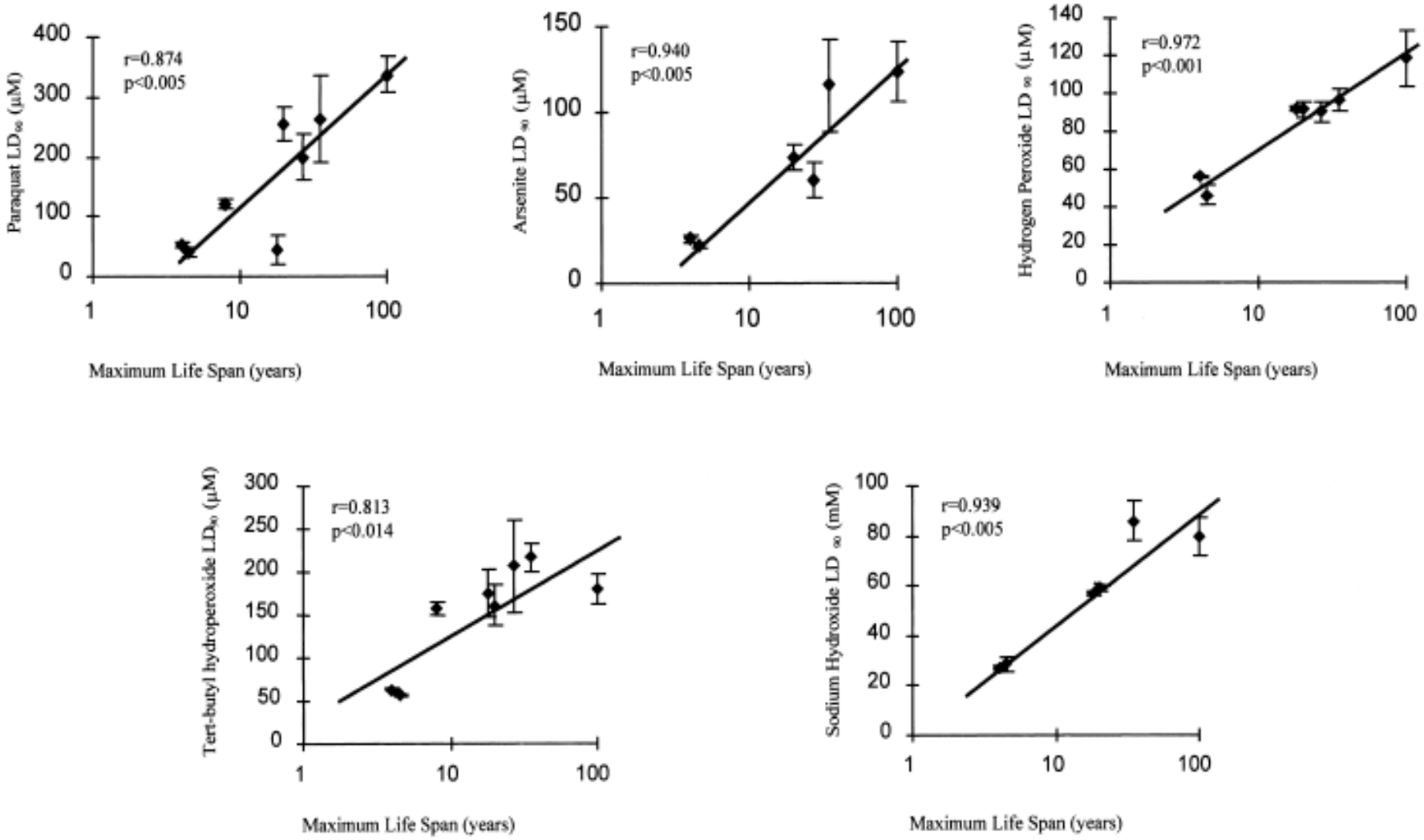
- Hydra can reproduce sexually but mainly reproduce by budding
- Any part can regenerate the whole
- Germ cells permeate the entire structure
- Therefore, Hydra has no true soma to be disposable

EVOLUTION OF LONGEVITY

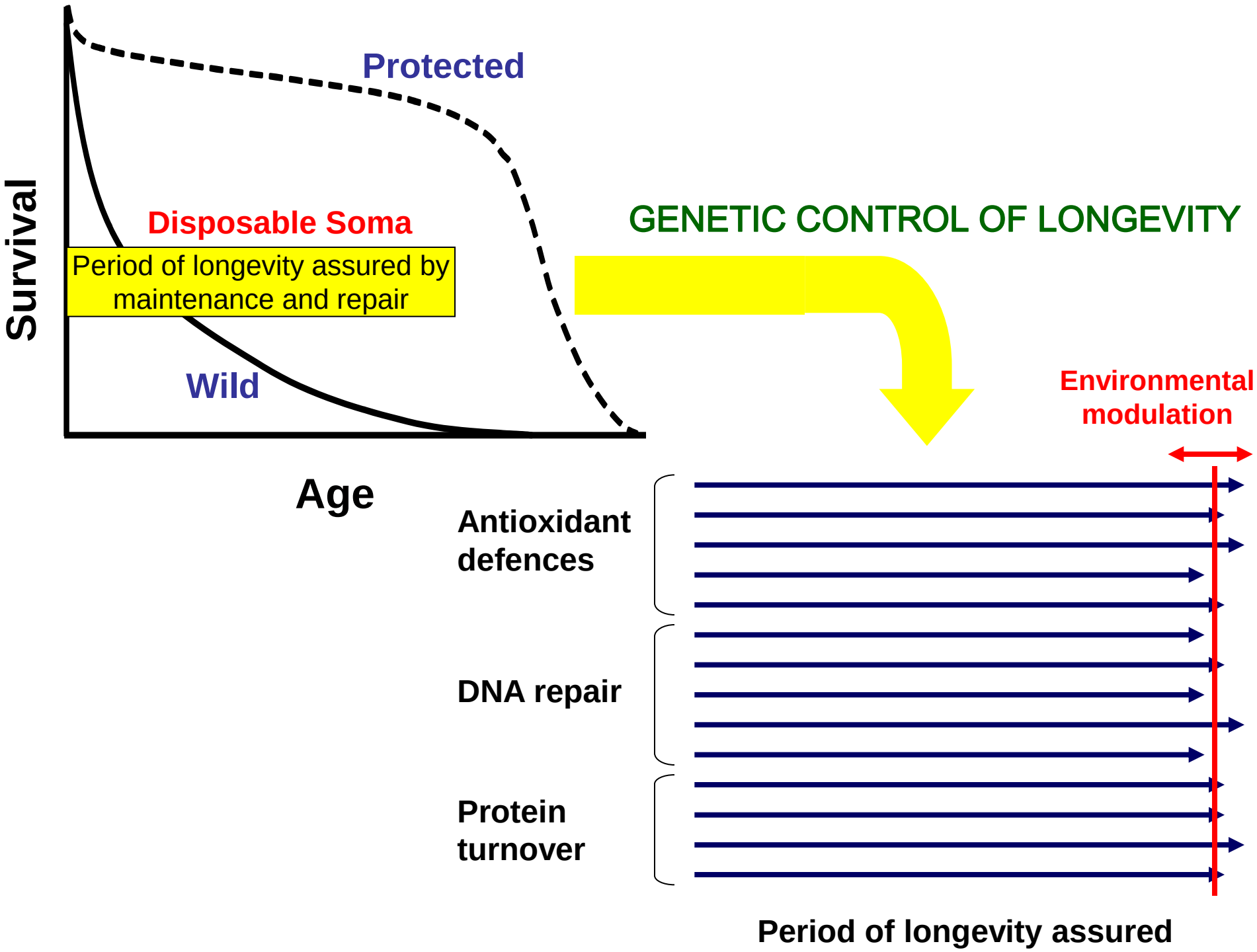


Acquisition of an adaptation (e.g. flight) that reduces extrinsic mortality)

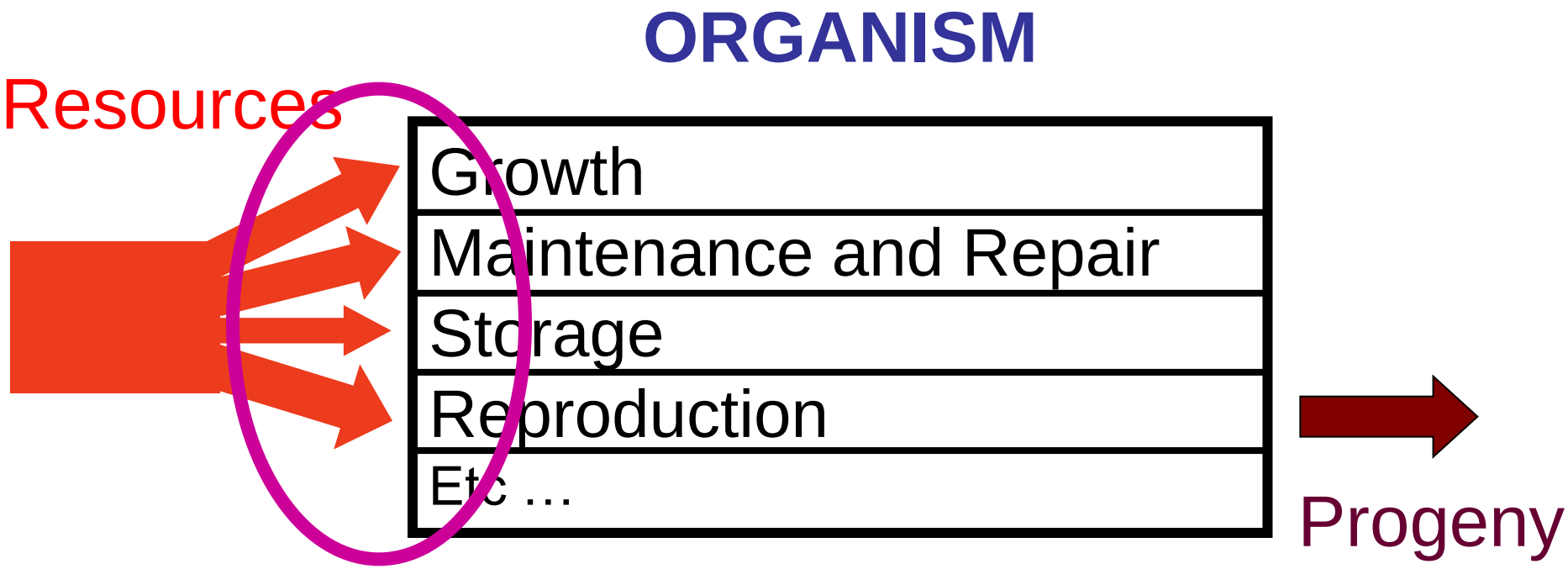
Correlation Between Cellular Stress Resistance and Mammalian Species Life Span



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

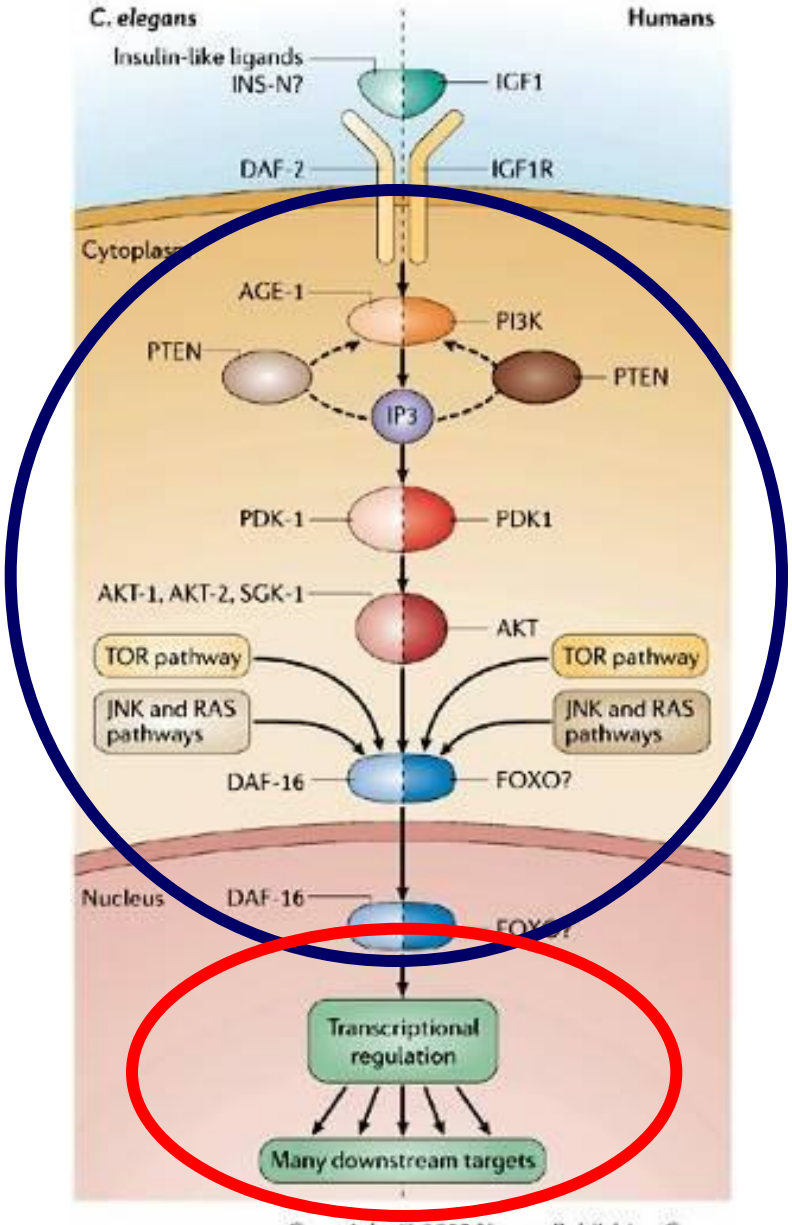

Protected
Survival
Disposable Soma
Period of longevity assured by maintenance and repair
Wild
Age
GENETIC CONTROL OF LONGEVITY
Environmental modulation
Antioxidant defences
DNA repair
Protein turnover
Period of longevity assured

THE CENTRAL ROLE OF METABOLISM - RESOURCE ALLOCATION AND FITNESS



Insulin/IGF-1 signalling promotes growth and storage.
Low insulin/IGF-1 promotes cell maintenance.

P66 affects storage (fat deposition) and lifespan



Longevity phenotype

Ageing phenotype

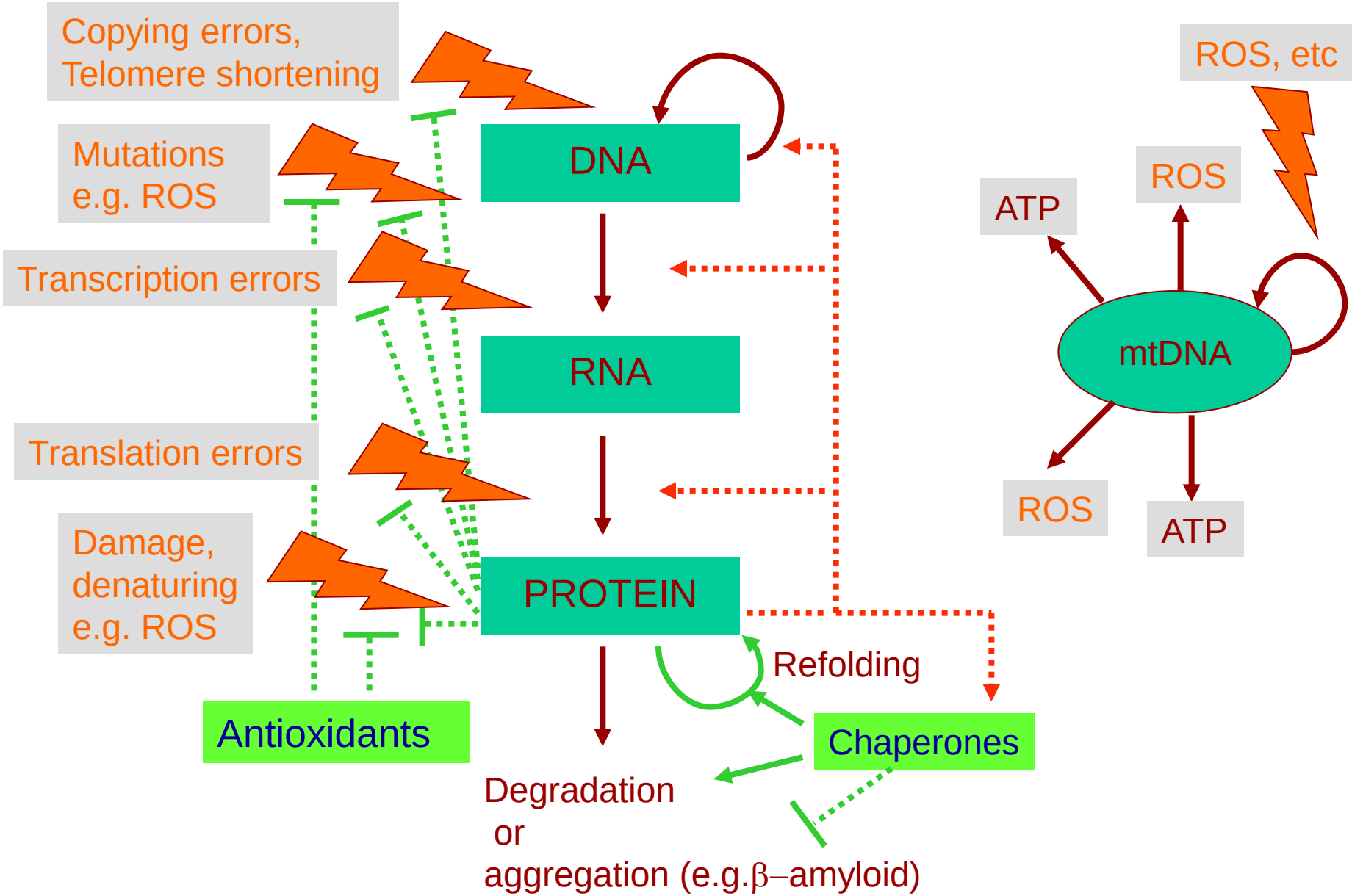
Christensen *et al. Nature Reviews Genetics* 2006

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

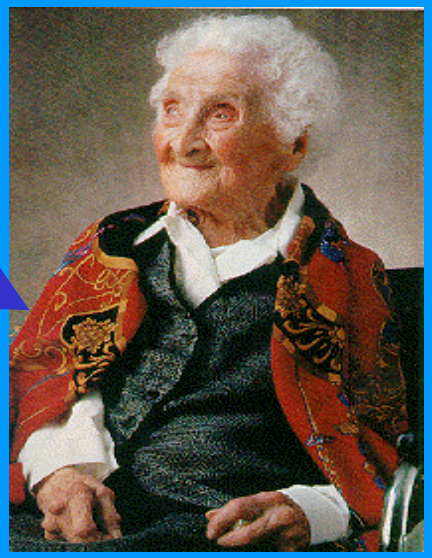
- Inherently stochastic
- Multiple mechanisms; Complexity
- Plasticity and trade-offs

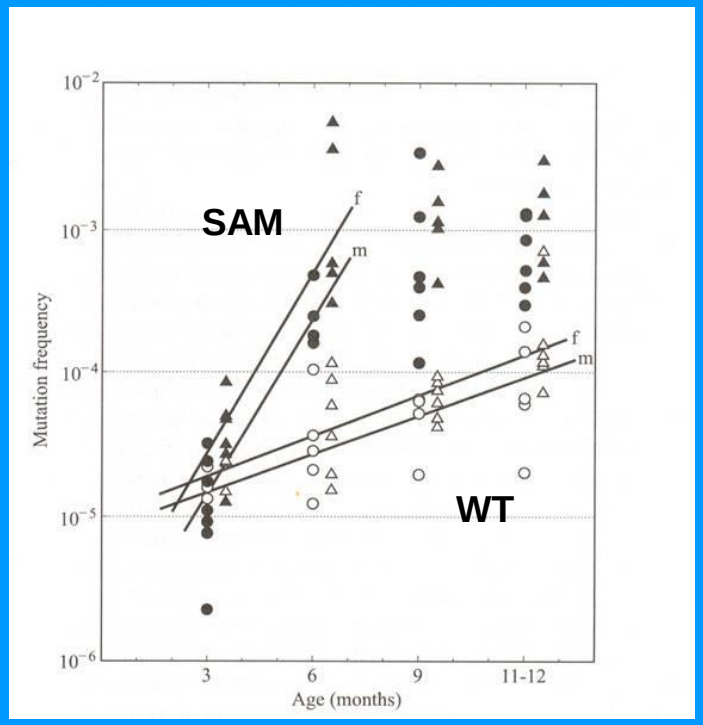
Primary Mechanisms of Ageing



Damage Accumulates From Day One

Each cell division is accompanied by inevitable somatic mutation

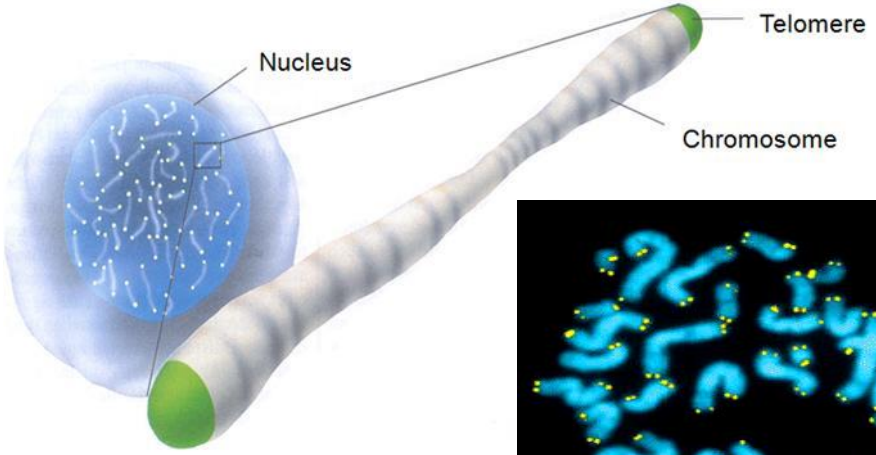


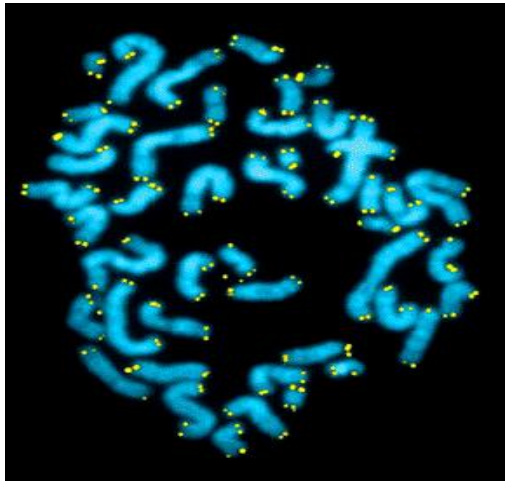


Age-Related Increase in Frequency of *Hprt* Mutations in Mice

Odagiri et al *Nat Genet* 1998

Telomere Erosion



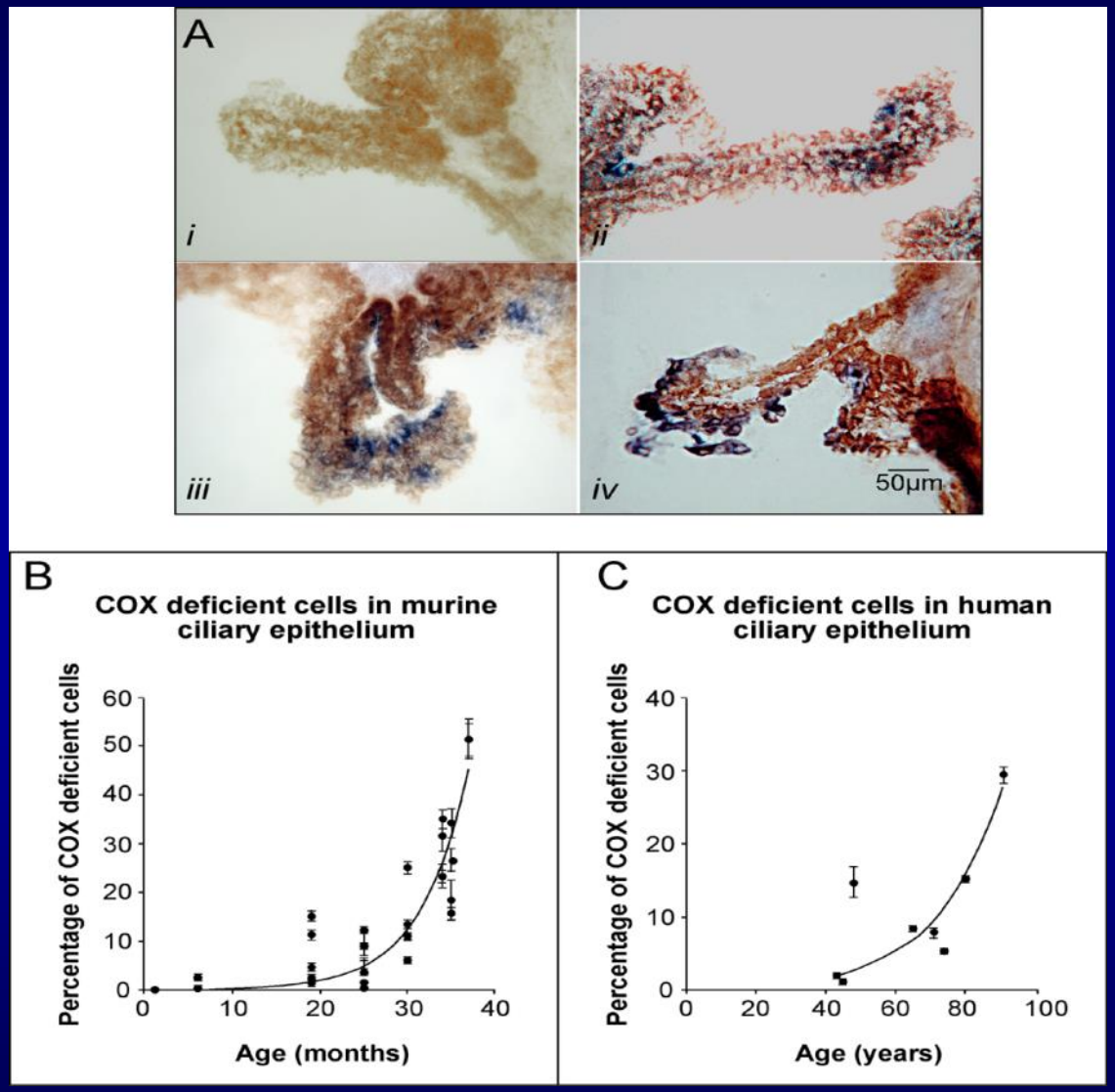


- Telomeres protect chromosome ends – they shorten with cell division (end-replication problem); and this is accelerated by biochemical stress.
- Critically short telomeres cause growth arrest.
- Prematurely short telomeres are linked with <u>increased risk of age-related disease</u> and <u>diminished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

<u>Telomerase</u>

- Protects against end-replication problem.
- Inactive in most somatic cells.
- Active in germ-line, stem cells and most cancers.

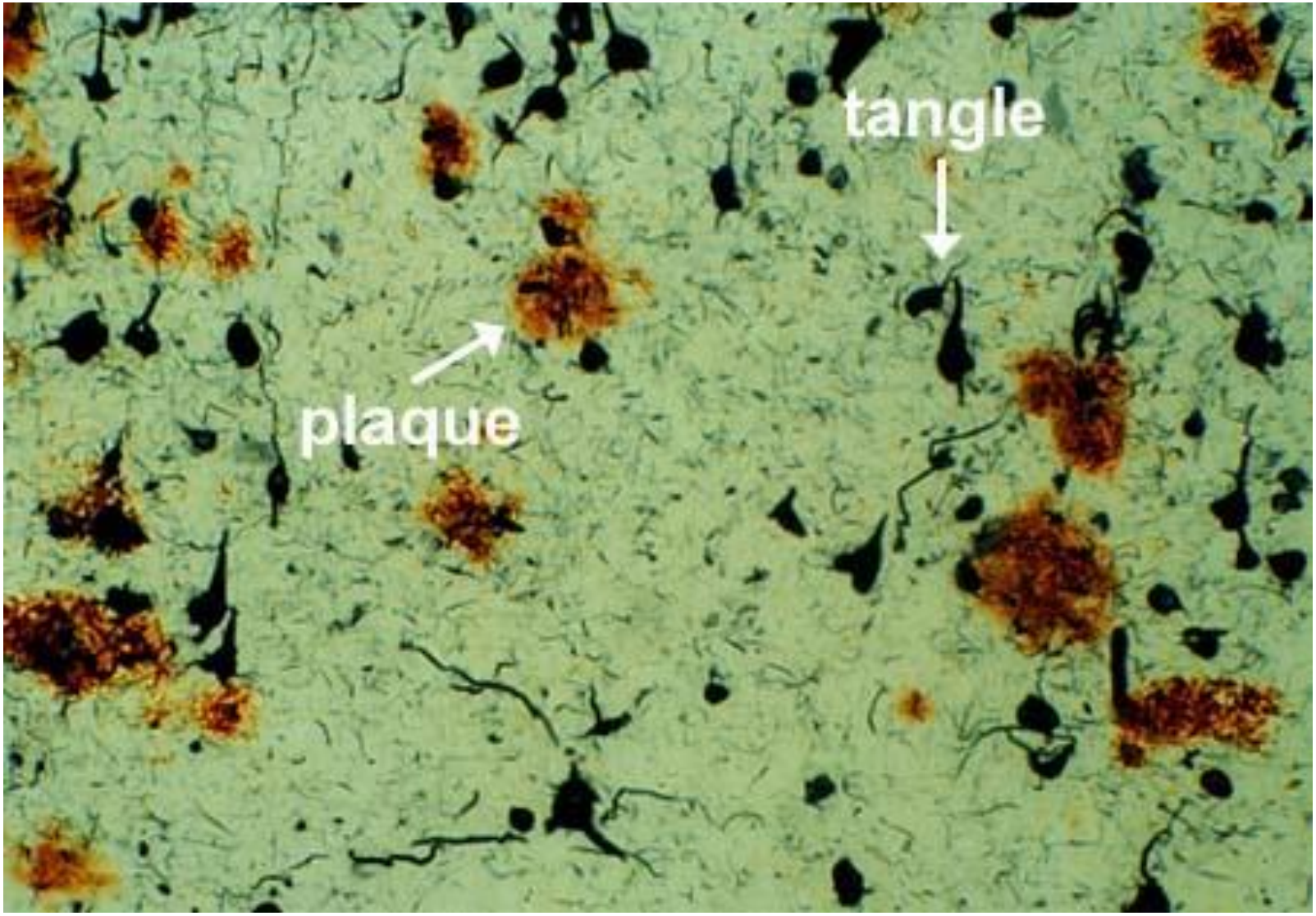
Mitochondrial Mutations Accumulate with Ageing



Ciliary epithelium (eye)

Greaves et al *Mech. Aging Dev.* 2011

Abnormal Protein Aggregation in Ageing Brain



The Ageing Process

Functional Impairments in Organs and Tissues leading to Age-related Frailty, Disability, and Disease

↕

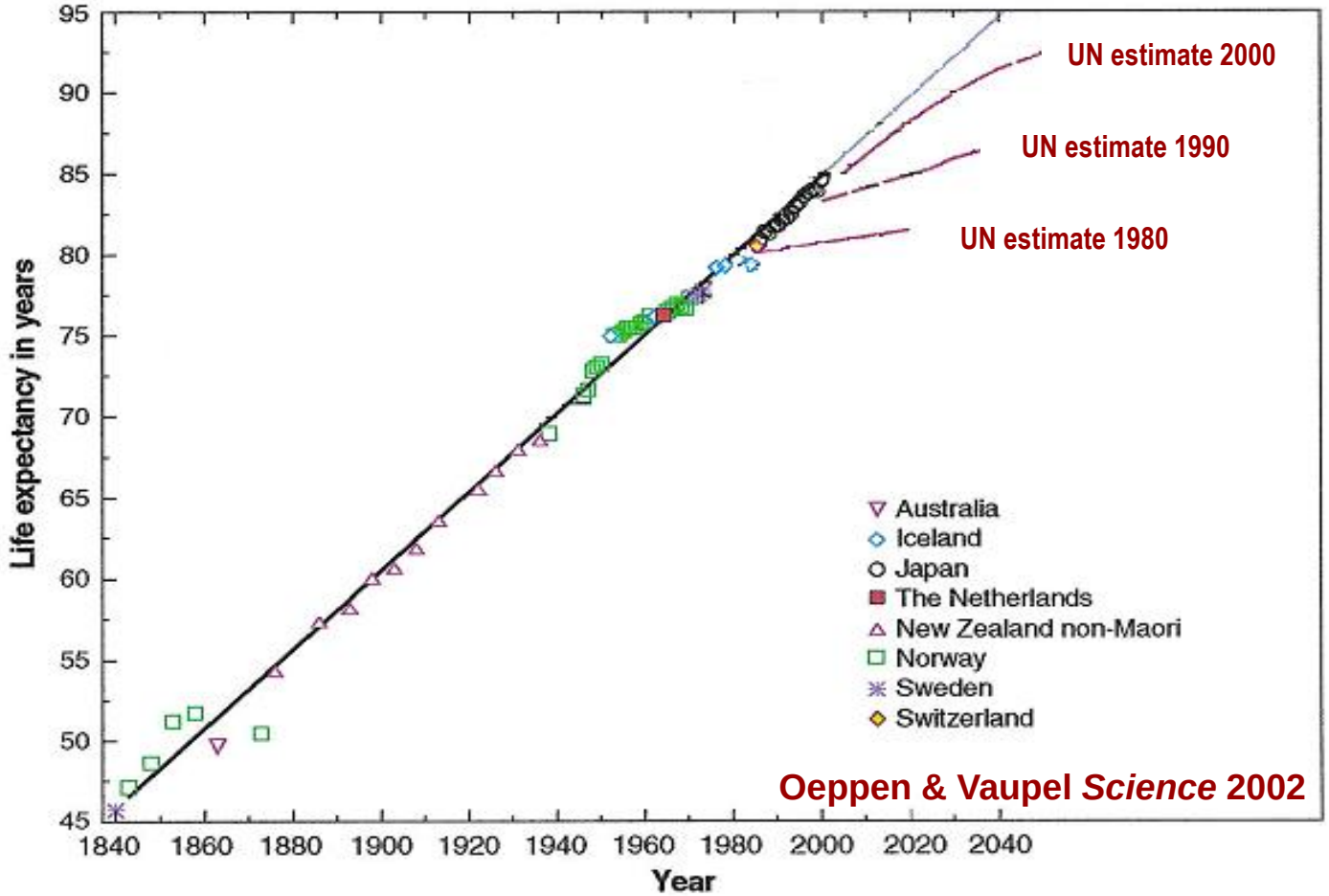
Accumulation of Cellular Defects

↑ ↑ ↑ ↑ ↑

Random Molecular Damage

What is driving the current increase in longevity?

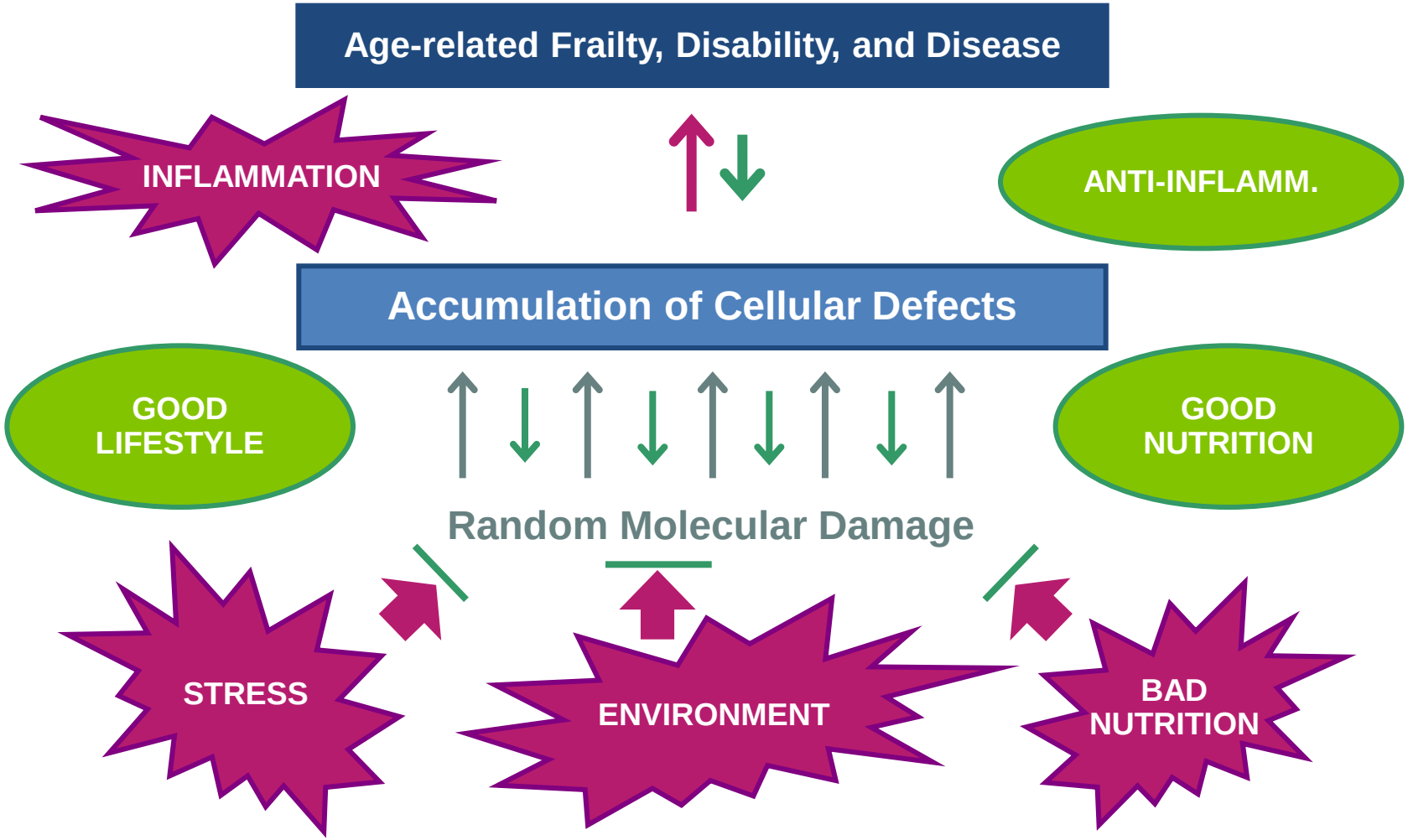
The Continuing Increase in Life Expectancy



Declining early/mid-life mortality → Declining later-life mortality →

AGEING PROCESS AND ITS MALLEABILITY

Kirkwood *Cell* 2005



Back to Those Special Cases

- Pacific salmon
- Menopause

The Necessary Logic for an Evolutionary Hypothesis

- Precise
- Viable
- Quantitative

Evolution Works by Numbers!!!

Pacific Salmon

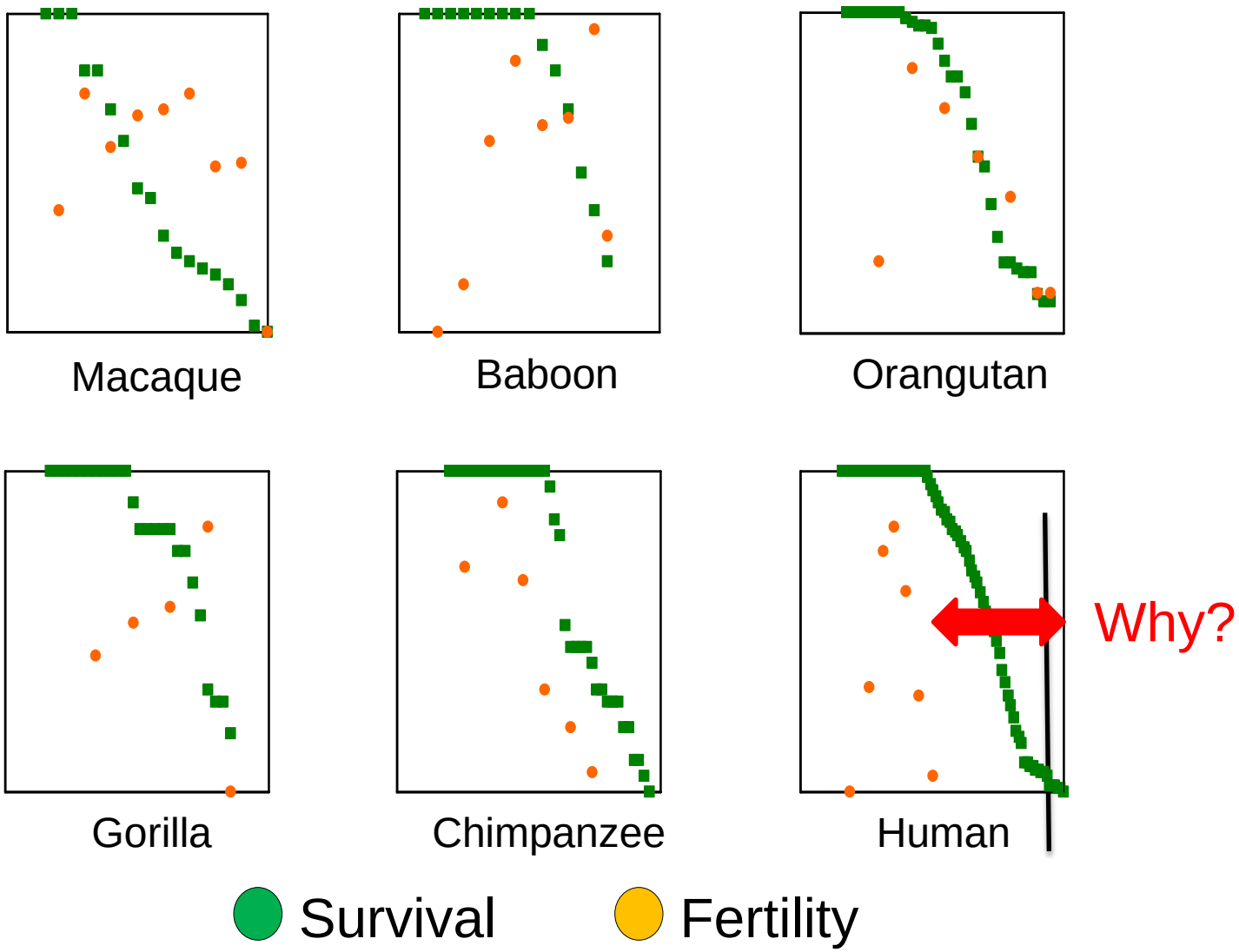
Death occurs rapidly following the organism's one and only bout of reproduction (semelparity).

The life cycle of a semelparous organism comprises a long phase of growth, during which it prepares for reproduction.

When the signal to reproduce comes, the organism must direct all available effort at maximising reproductive success, <u>regardless of consequences for long-term survival</u>.

An extreme example of the "disposable soma".

The Uniqueness of the Human Menopause



Caro et al. (1995) *Int J Primat* 16, 205-220

Big Brains, Big Dilemma

The driving force behind human longevity is the evolution of a big brain. But big brains have two major drawbacks:

1). They make it harder to give birth safely.

- For older mothers, the risks associated with childbirth increase steeply.

2). They take longer to programme.

- Death of the mother will make the survival of her dependent children unlikely.

Maternal Mortality Hypothesis

The Darwinian Importance of Grandmothers

- Post-reproductive females assist their daughters in support of their grandchildren.

- In this way, grandmothers may promote their genes better than by having more children of their own.

Grandmother Hypothesis

Why Menopause Evolved?

- Neither the ‘maternal mortality’ nor the ‘grandmother’ hypothesis makes a big enough numerical contribution to account for the evolution of menopause by itself.

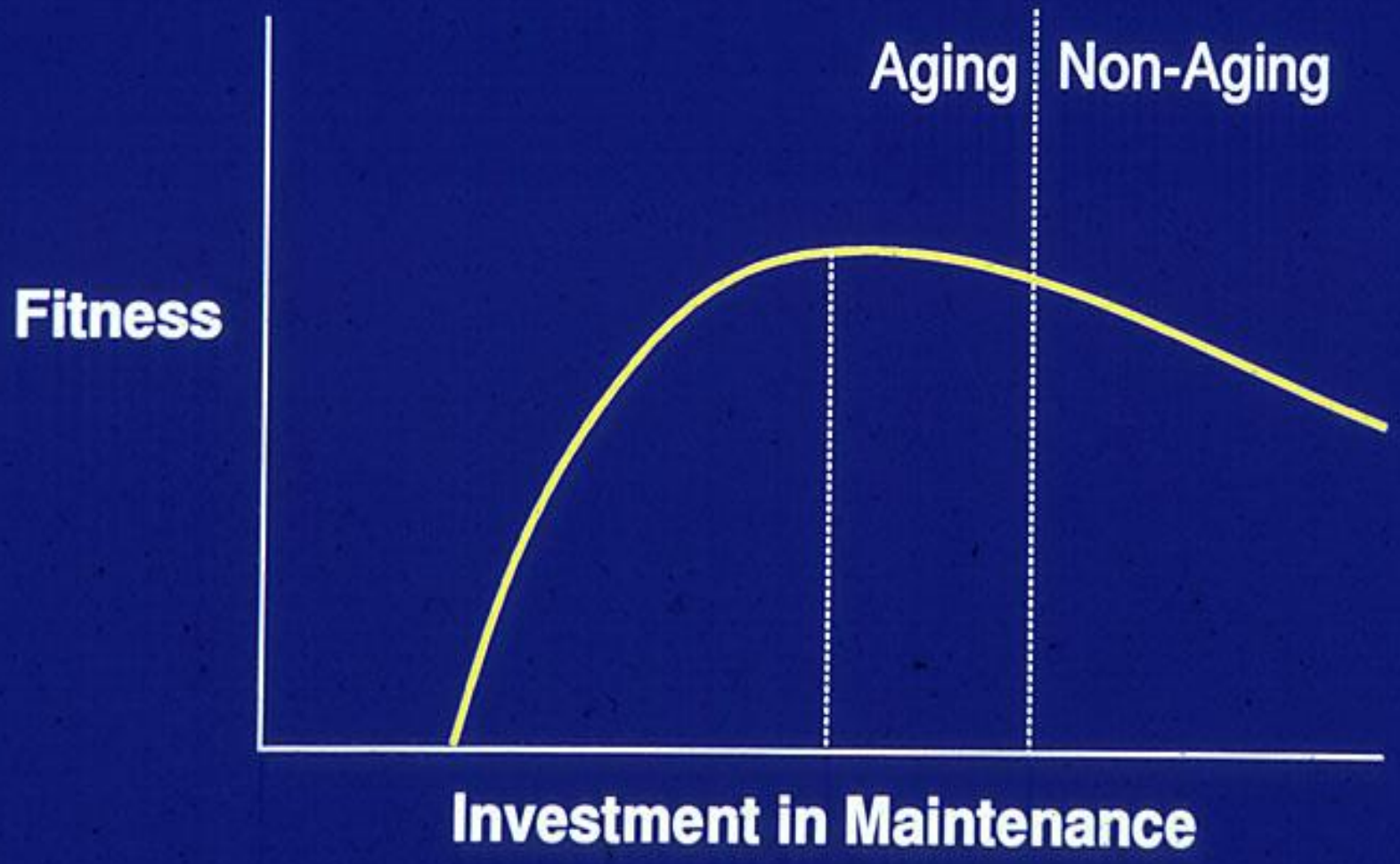
- BUT, putting both mechanisms together can explain why menopause evolved.

- The requirement for both mechanisms acting together also explains the uniqueness of the human menopause.

Shanley & Kirkwood *BioEssays* 2001
Shanley et al *Proc Roy Soc* 2007

Is human longevity still evolving?

Optimising the Investment in Maintenance



Human Longevity versus Reproductive Success

- 33,497 British aristocrats born pre-1876 with records of birth, marriage, children, death.

- Women who died aged 80 or older showed:
  - higher levels of infertility
  - later first childbirths
  - smaller family sizes

than women who died at younger ages.

Westendorp & Kirkwood *Nature* 1998

Trade-off Affecting Human Reproduction and Survival

- Women with impaired fertility exhibit a heritable immune profile that makes them less susceptible to fatal infectious disease.

  Westendorp et al *Nature Medicine* 2001

- The advantage of increased survival is thus traded against decreased family size.

- In recent times, as human reproductive patterns and the mortality pressure imposed by infection are changing, this balance is likely to alter.

  Drenos et al *Biogerontology* 2006

- … and menopause is likely to be postponed as well, but don’t wait for this!!!

Conclusions

Ageing makes sense only in the light of evolution.

Ageing results primarily from damage, because natural selection never placed high enough priority on maintaining our bodies to last forever.

This view helps us to understand the actions of genetic as well as non-genetic factors in influencing longevity.

Menopause most likely reflects the unique emergence of ageing in “the wild” during recent human evolution and reflects the special value of older women.

The evolutionary balance might be shifting.

“If I’d known I was going to live this long, I’d have taken better care of myself”

US jazz musician Eubie Blake on the occasion of his 100th birthday