

Understanding the biology of ageing



Caenorhabditis elegans



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A scientific revolution in the biology of ageing



Evolution of
ageing



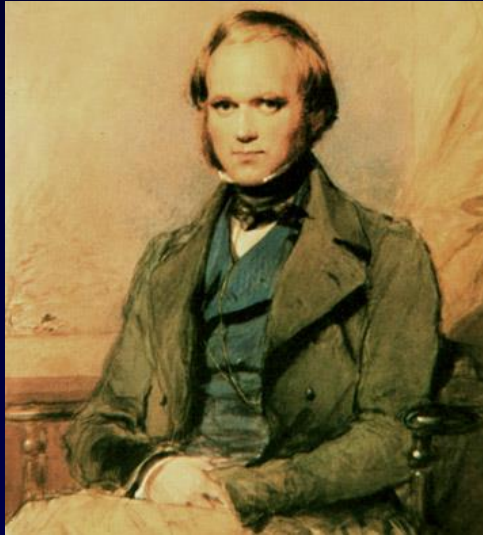
Mechanisms of
ageing



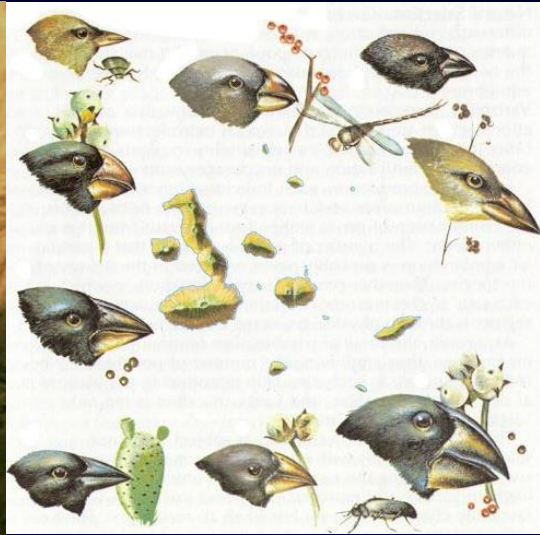
Genetics of
ageing



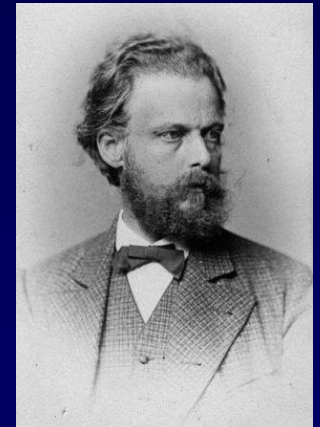
Interventions that
slow ageing



Charles Darwin



Galapagos finches

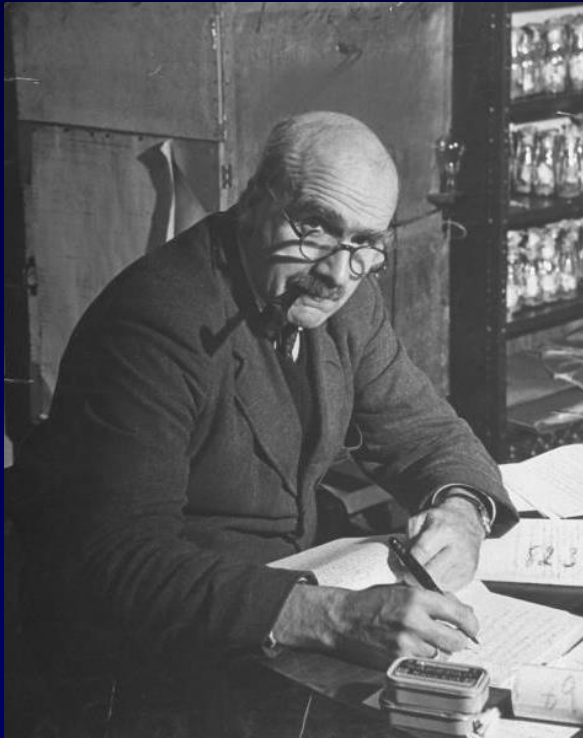


August
Weismann

What is ageing for?



Huntington's disease and the evolution of ageing



J.B.S. Haldane

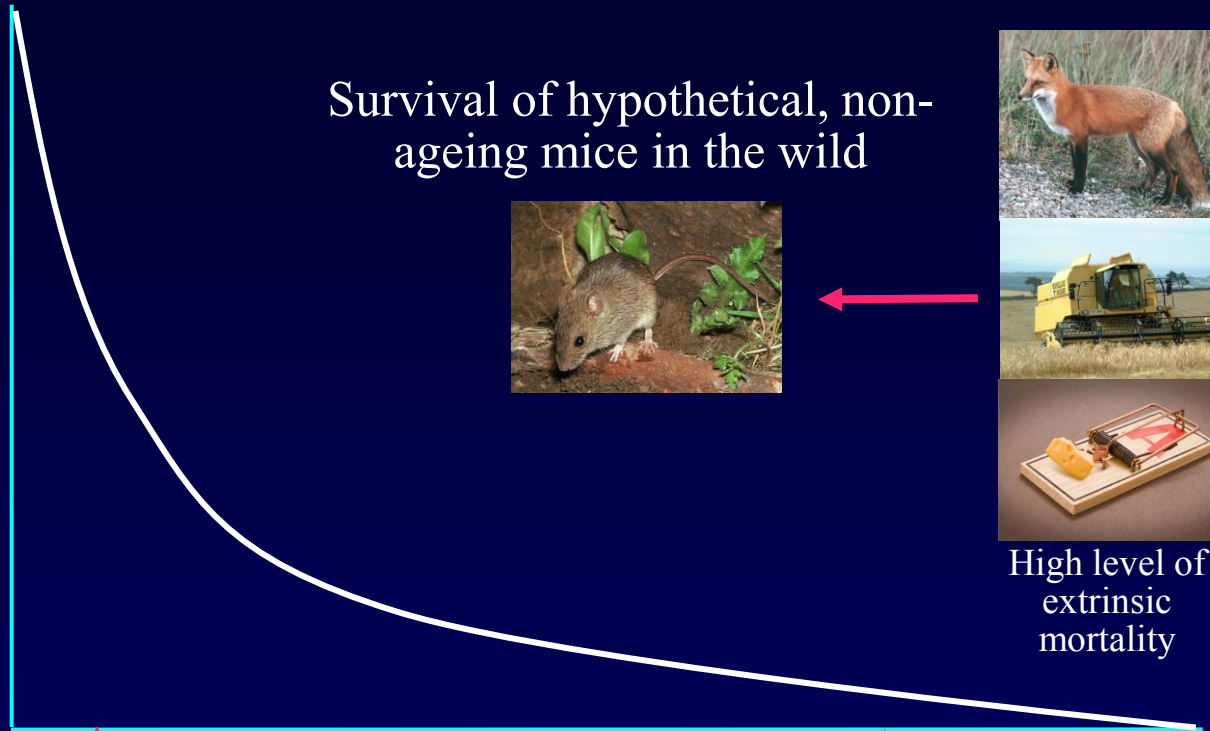
- Caused by a highly penetrant dominant mutation
- Haldane (1941): why has natural selection not acted to remove the Huntington's mutation from populations?
- Average age of onset of Huntington's 35.5 years
- For much of the evolutionary history of mankind, most people did not live to be that old
- The selective pressure to remove the Huntington's mutation is therefore weak
- **This establishes a principle: Mutations with deleterious effects in late life are subject to a weaker force of natural selection**

Evolution of ageing: The mutation accumulation theory



**Peter
Medawar**

Number alive



Survival of hypothetical, non-ageing mice in the wild



High level of
extrinsic
mortality

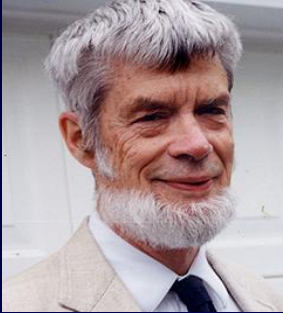
Early acting mutation,
most bearers still alive,
strong force of
natural selection

Late acting mutation,
few bearers still alive,
weak force of
natural selection

Mutations with late life deleterious effects will accumulate in populations

These accumulated mutations cause ageing

The trade-off theory for the evolution of ageing



George C.
Williams

- Mutations may be beneficial in youth, but at the price of a higher rate of ageing
- More individuals will survive to express the early benefit than will survive to suffer the higher rate of ageing
- Such mutations can be incorporated by natural selection

Ageing evolves as a side-effect of natural selection in favour of mutations that are beneficial during youth









Ageing:

Not an adaptation

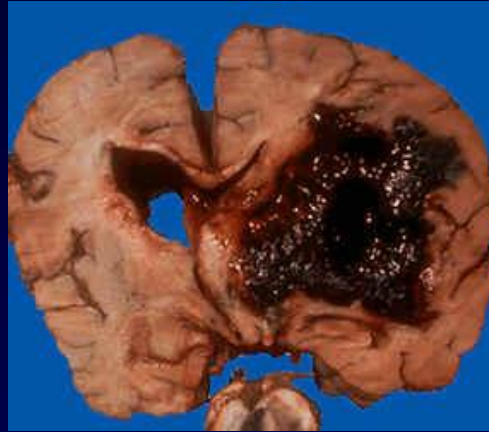
Not *programmed*

A genetic disease (c.f. HD)

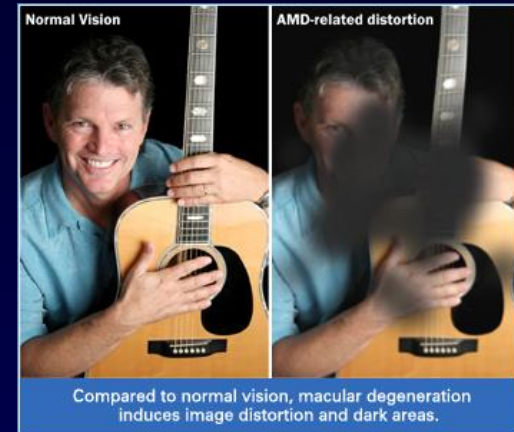
Ageing: a genetic disease syndrome

| Normal Mole | Melanoma | Sign | Characteristic |
|---|---|-----------|---|
|  |  | Asymmetry | when half of the mole does not match the other half |
|  |  | Border | when the border (edges) of the mole are ragged or irregular |
|  |  | Color | when the color of the mole varies throughout |
|  |  | Diameter | if the mole's diameter is larger than a pencil's eraser |

Cancer



Stroke



Macular degeneration

Iris
Murdoch



Alzheimer's Disease



Type II diabetes



Urinary incontinence



“Ageing is not
a disease”



A duck

Ageing *is* a disease

...and so it is the duty of doctors to treat it

Aging (senescence): the set of endogenously generated pathologies that increase in later life

D. Gems, *Exp. Gerontol.* 2014 58: 14-18

Subject: Finally, an advert that celebrates ageing
From: Age UK <ageuk@mailier.ageuk.org.uk> ▼



'Ageing is not an illness but a way of life'
Watch how our new TV advert celebrates ageing



Subject: Finally, an advert that celebrates ageing
From: Age UK <ageuk@mailier.ageuk.org.uk> ▼



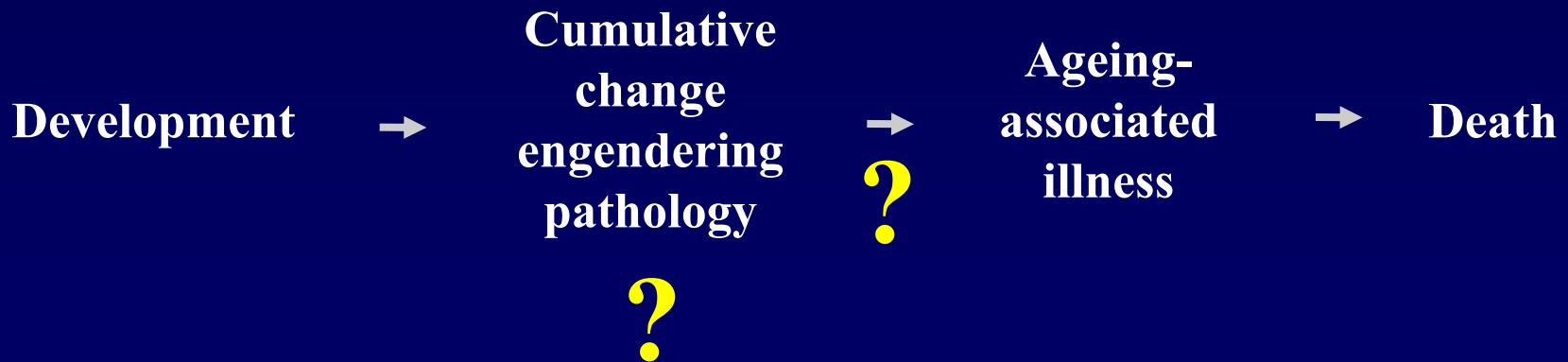
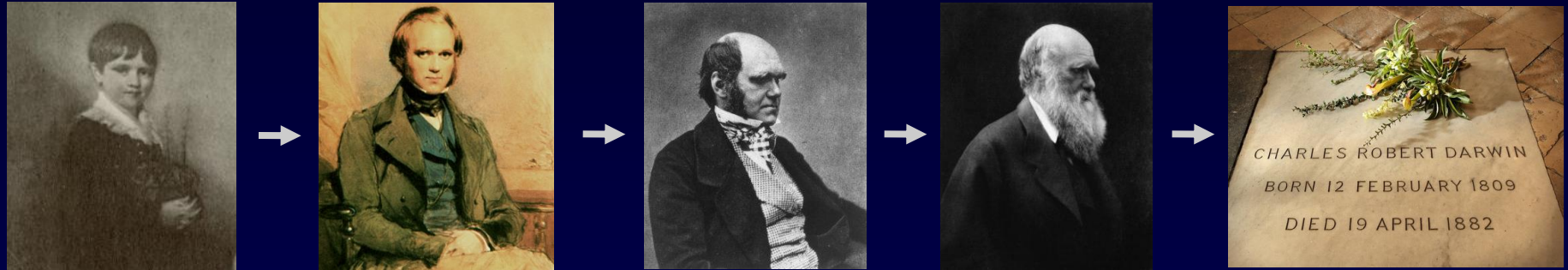
'Dementia is not an illness but a way of life'
Watch how our new TV advert celebrates dementia



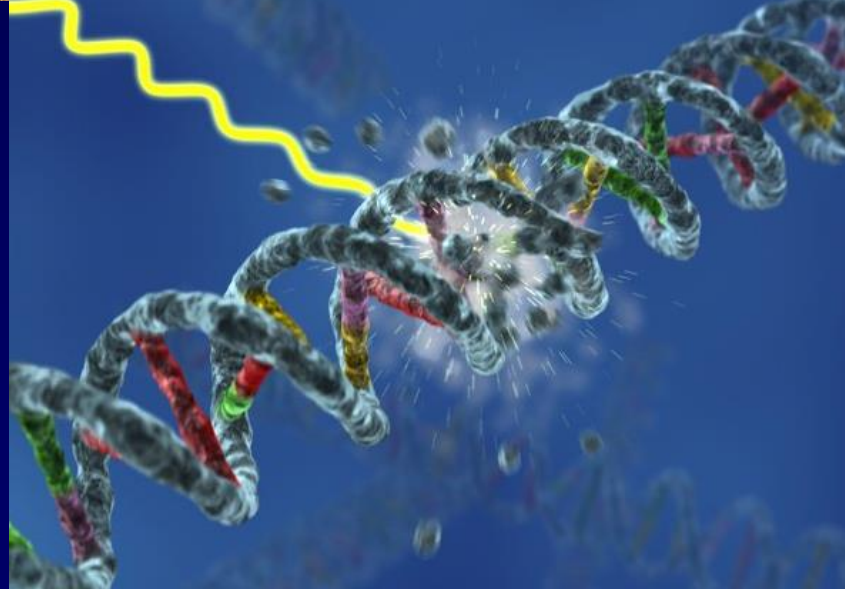
...Medical Research Council



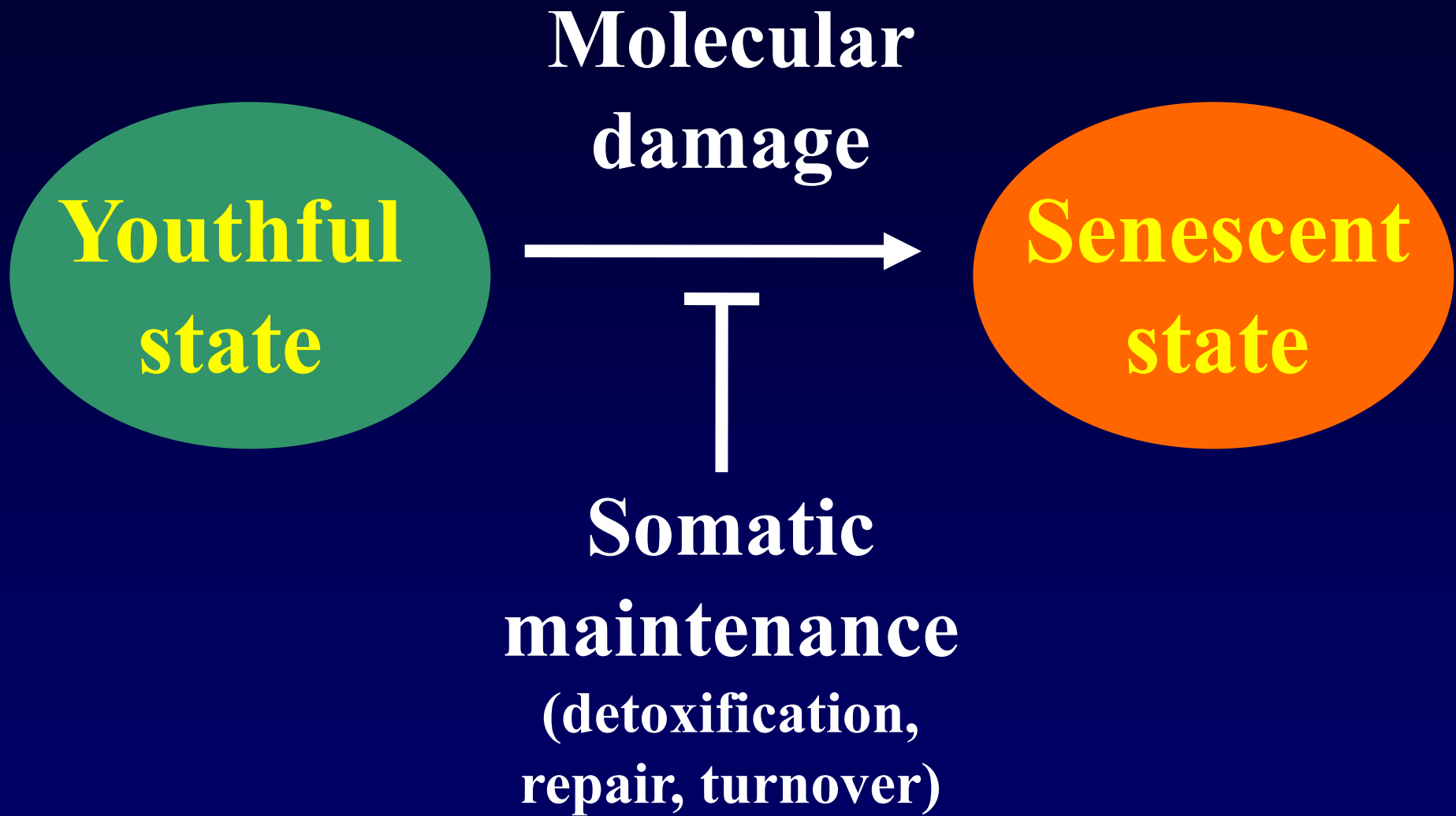
What is the mechanism of ageing?



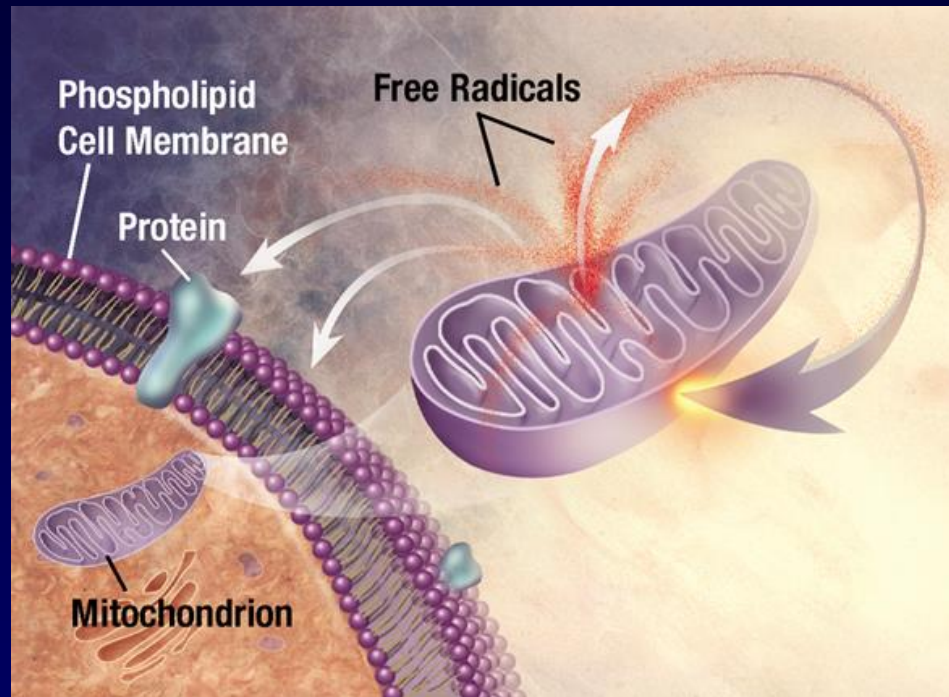
**Cumulative change =
wear and tear?**



Standard ageing paradigm



Oxidative damage theory of ageing

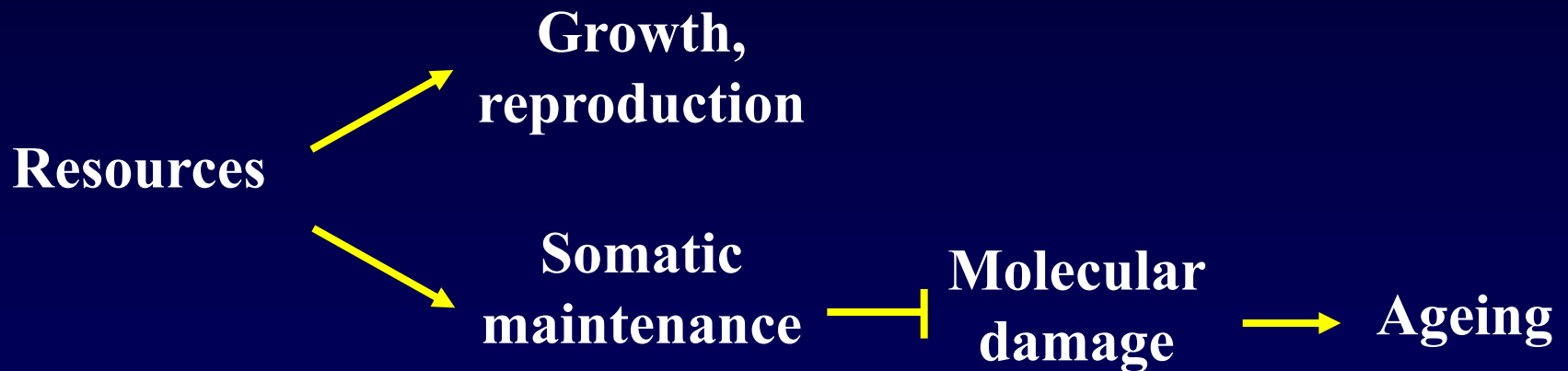


Superoxide free radical, O_2^- , e.g. from mitochondrial respiration causes molecular damage, ageing?



Tom Kirkwood

Integrating evolutionary and mechanistic theories of ageing



1977: Somatic maintenance is **costly** in resource terms

Resources invested in somatic maintenance are just sufficient to assure survival of the soma during reproduction

All remaining resources invested in growth, reproduction

Consequence: **A disposable soma**



Maximum lifespans in mammals



3 years

59 years

110 years

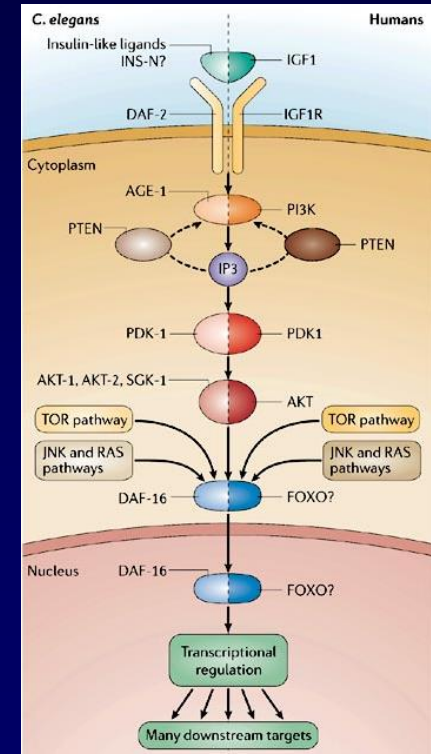
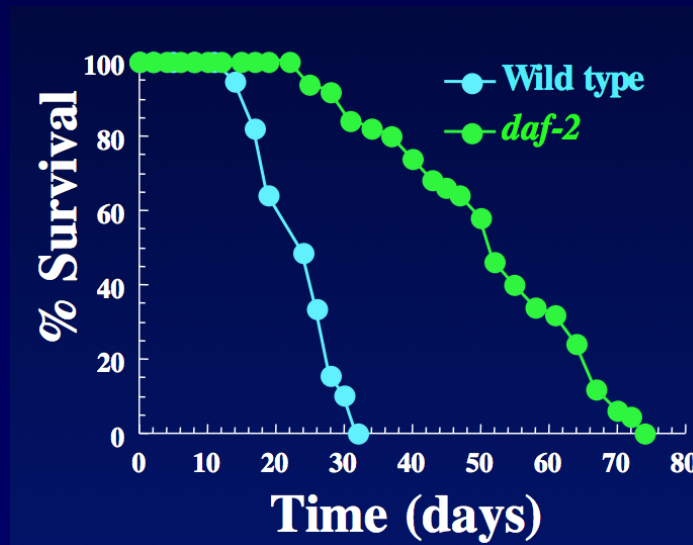
Ageing rate, lifespan are strongly influenced by genes



Caenorhabditis elegans

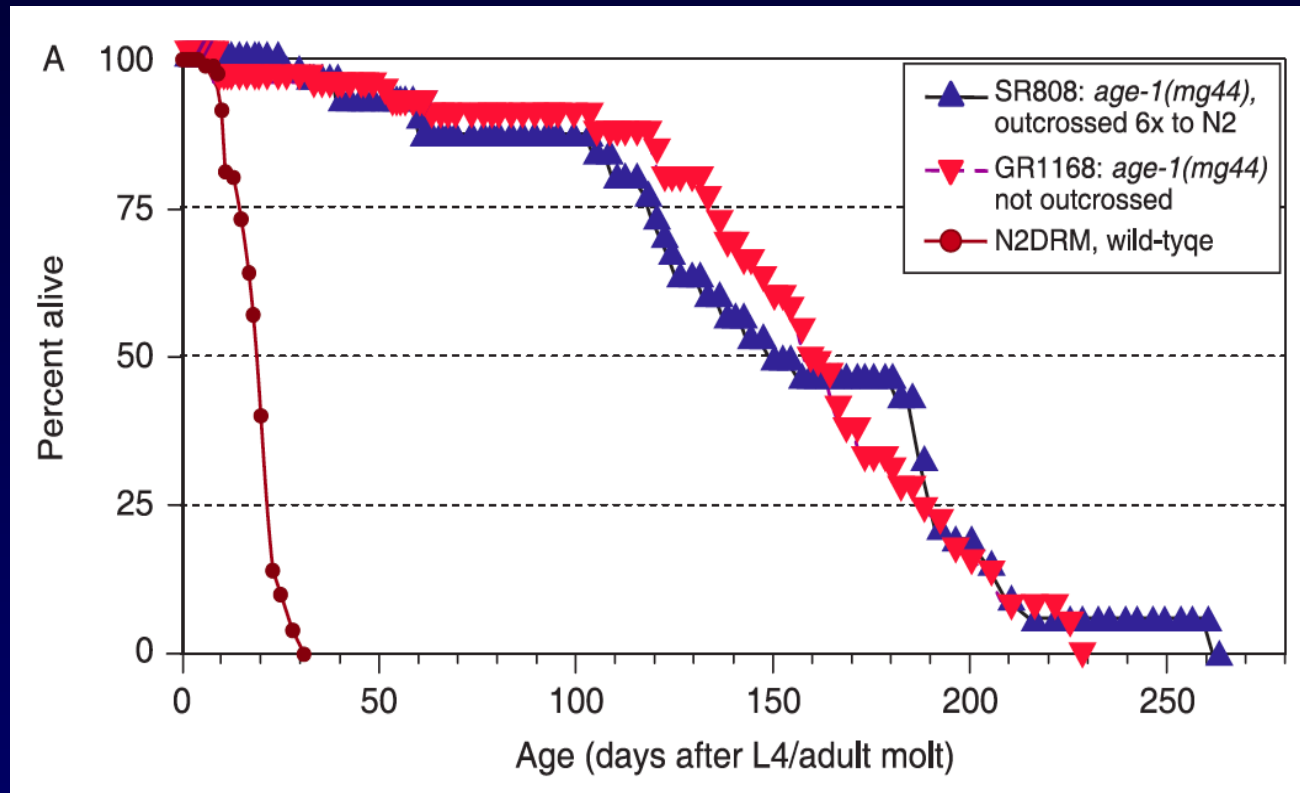
A nematode with a lifespan of 2-3 weeks
Identify mutants with altered ageing rate
Discover genes, gene products controlling ageing

Cynthia
Kenyon
1993



How does the insulin/IGF-1/TOR signalling network control ageing?

Ageing is plastic



Ayyadevara *et al.*
Aging Cell 2007

A *C. elegans* mutant with a 10-fold increase in lifespan!

*Another intervention
that slows ageing*

Dietary restriction



60-70% *ad libitum* food levels

Sufficient vitamins, minerals

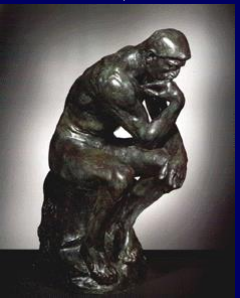
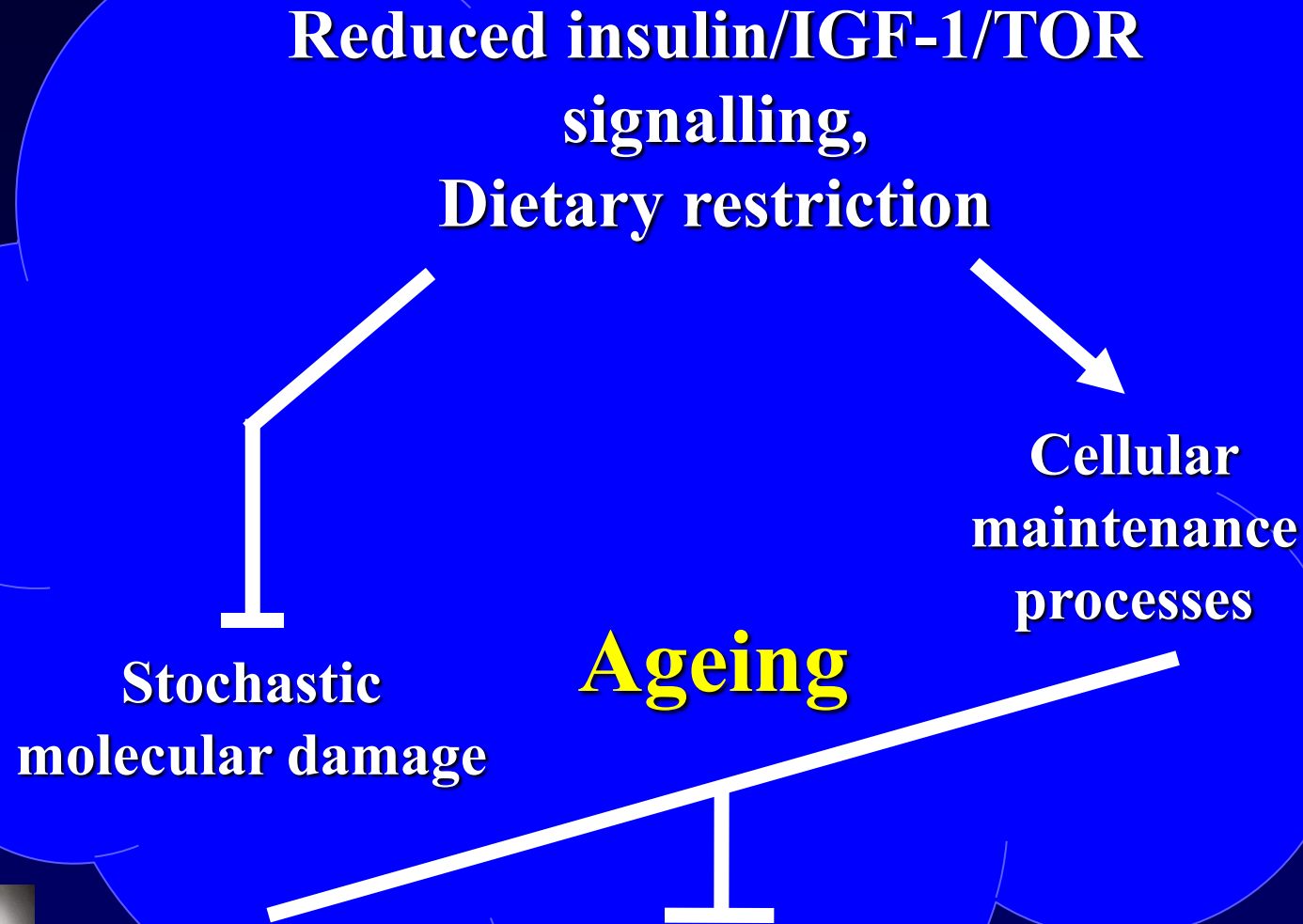
20-40% increase in lifespan (McCay et al 1935)

Protects against age-related disease

Extension of ‘youthspan’

How does DR slow ageing?

Working model





Milicianas, 1936





Problems with the working model

- Mechanism of action of IIS/TOR and DR remain unsolved
- Little evidence for partitioning of energy between reproduction and somatic maintenance
- Does molecular damage actually cause ageing?

Crisis in the oxidative damage theory of ageing

GENES & DEVELOPMENT 22:3236–3241 © 2008

Against the oxidative damage theory of aging: superoxide dismutases protect against oxidative stress but have little or no effect on life span in *Caenorhabditis elegans*

Ryan Doonan,^{1,3} Joshua J. McElwee,^{1,3}
Filip Matthijssens,^{2,3} Glenda A. Walker,¹
Koen Houthoofd,² Patricia Back,²
Andrea Matscheski,¹ Jacques R. Vanfleteren,²
and David Gems^{1,4}

[Cell Cycle 8:11, 1-7; 1 June 2009]; ©2009 Landes Bioscience

Review

Antioxidant defense and aging in *C. elegans*

Is the oxidative damage theory of aging wrong?

David Gems and Ryan Doonan

Biochimica et Biophysica Acta 1790 (2009) 1005–1014



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Review

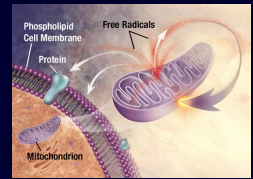
Is the oxidative stress theory of aging dead?

Viviana I. Pérez^{a,b}, Alex Bokov^{a,c}, Holly Van Remmen^{a,b,d,f}, James Mele^d, Qitao Ran^{a,b},
Yuji Ikeno^{a,e,f}, Arlan Richardson^{a,b,f,*}

ANTIOXIDANTS & REDOX SIGNALING
Volume 13, Number 12, 2010
© Mary Ann Liebert, Inc.
DOI: 10.1089/ars.2010.3215

Reactive Oxygen Species and Aging in *Caenorhabditis elegans*: Causal or Casual Relationship?

Jeremy Michael Van Raamsdonk and Siegfried Hekimi

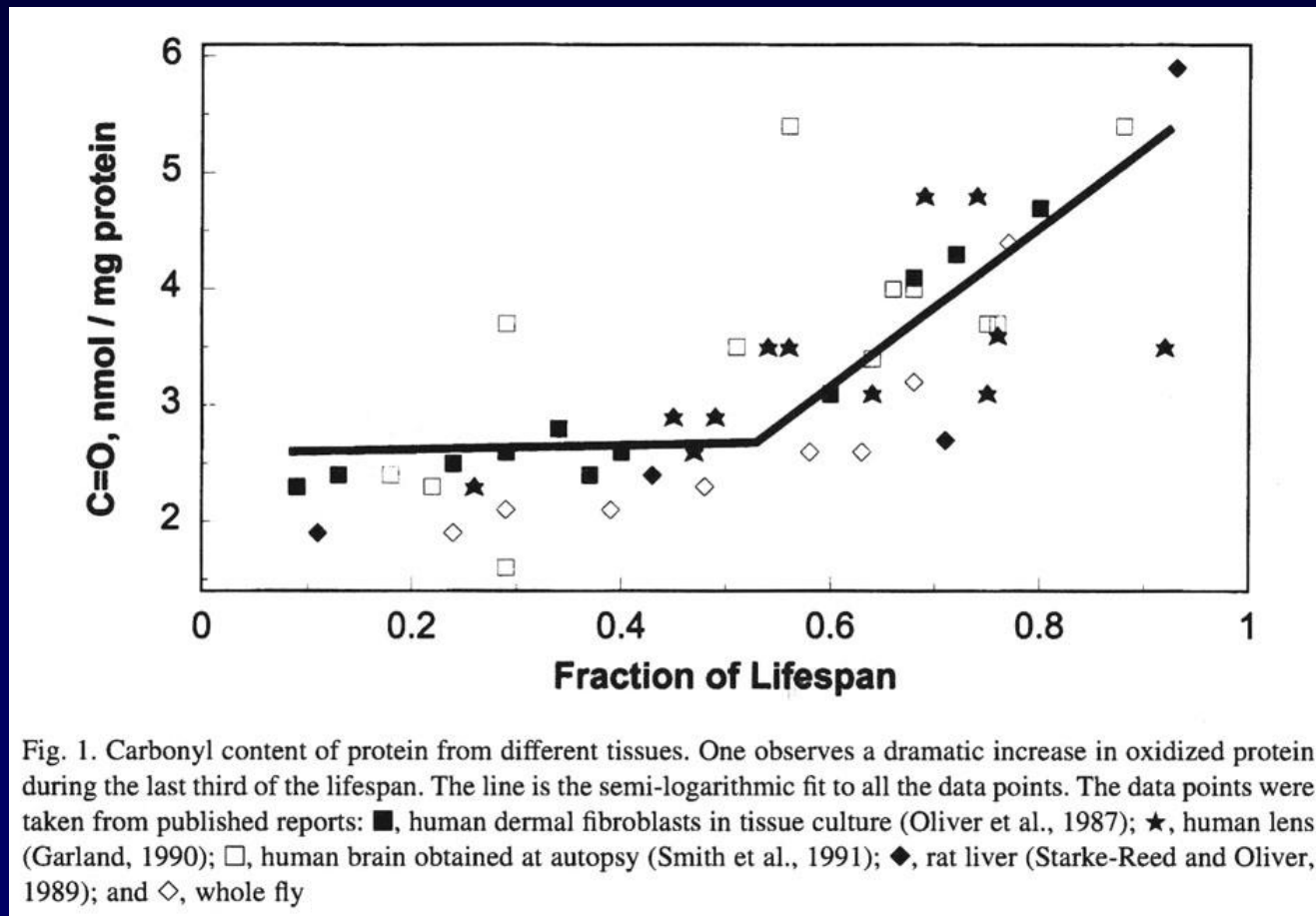


Against the oxidative damage theory

- Treatment with antioxidants does not slow ageing
- Overexpression of antioxidant enzymes does not slow ageing
- Reduced antioxidant defence can increase oxidative damage without affecting ageing
- Increased oxidative stress often increases lifespan

Evidence for the oxidative damage

Oxidative damage increases with increasing age



Correlation does not prove causality

“With age, I have accumulated a considerable knowledge regarding the oxidative damage theory. Does this knowledge cause my aging?”

M.V. Blagosklonny