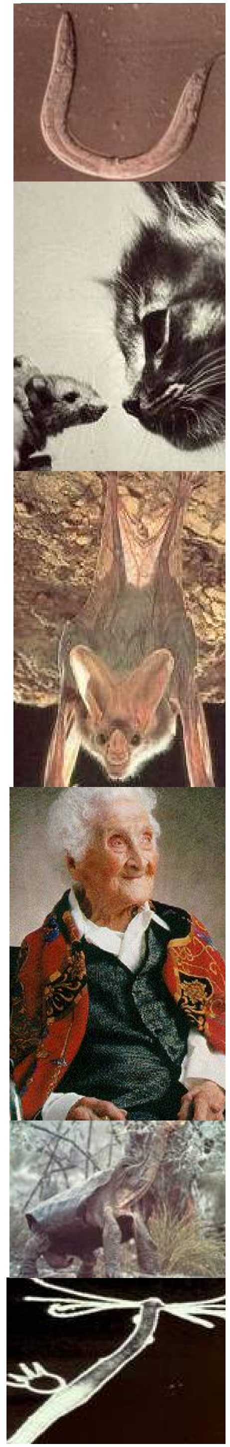
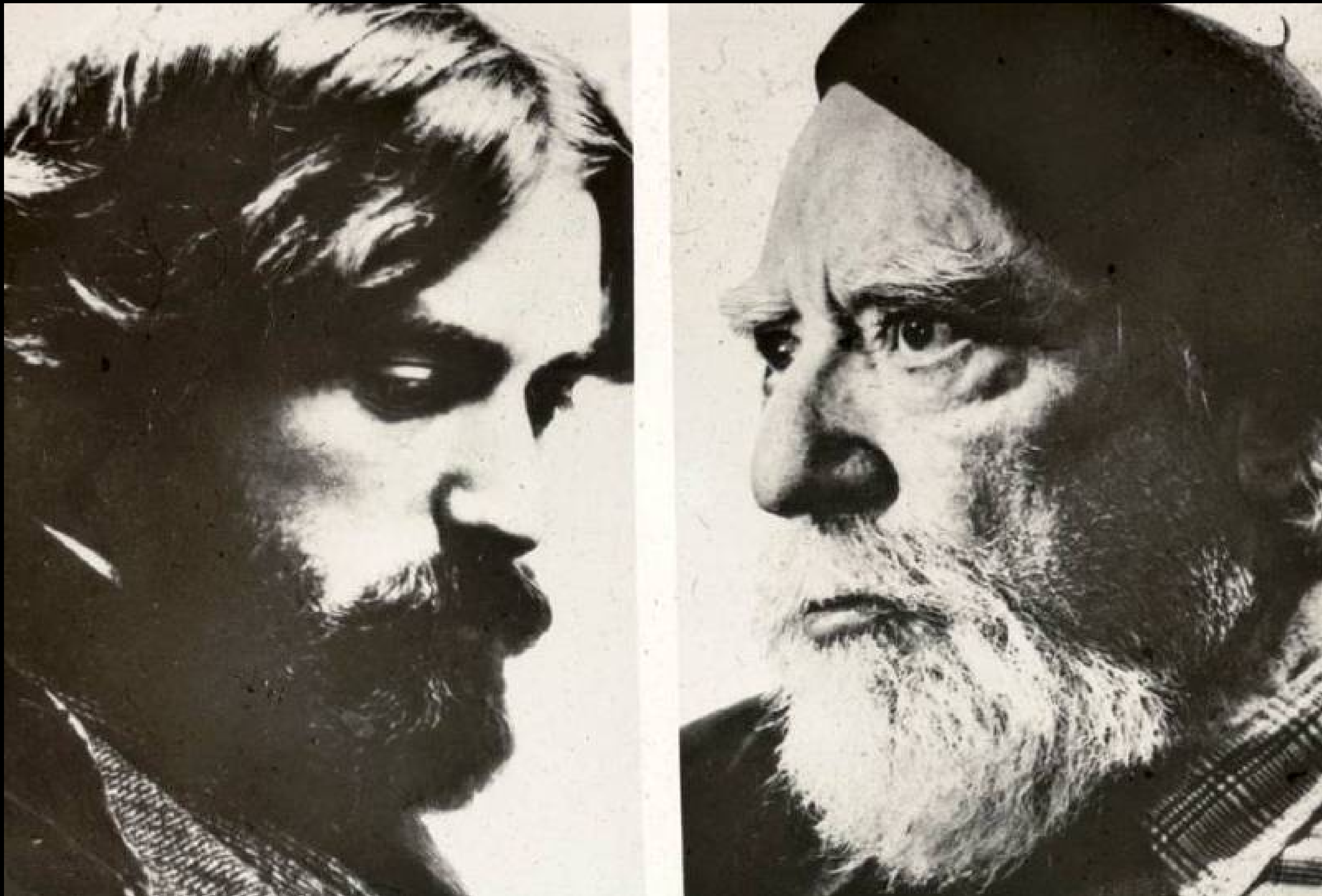
Systems Biology At Last: Ageing

Tom Kirkwood



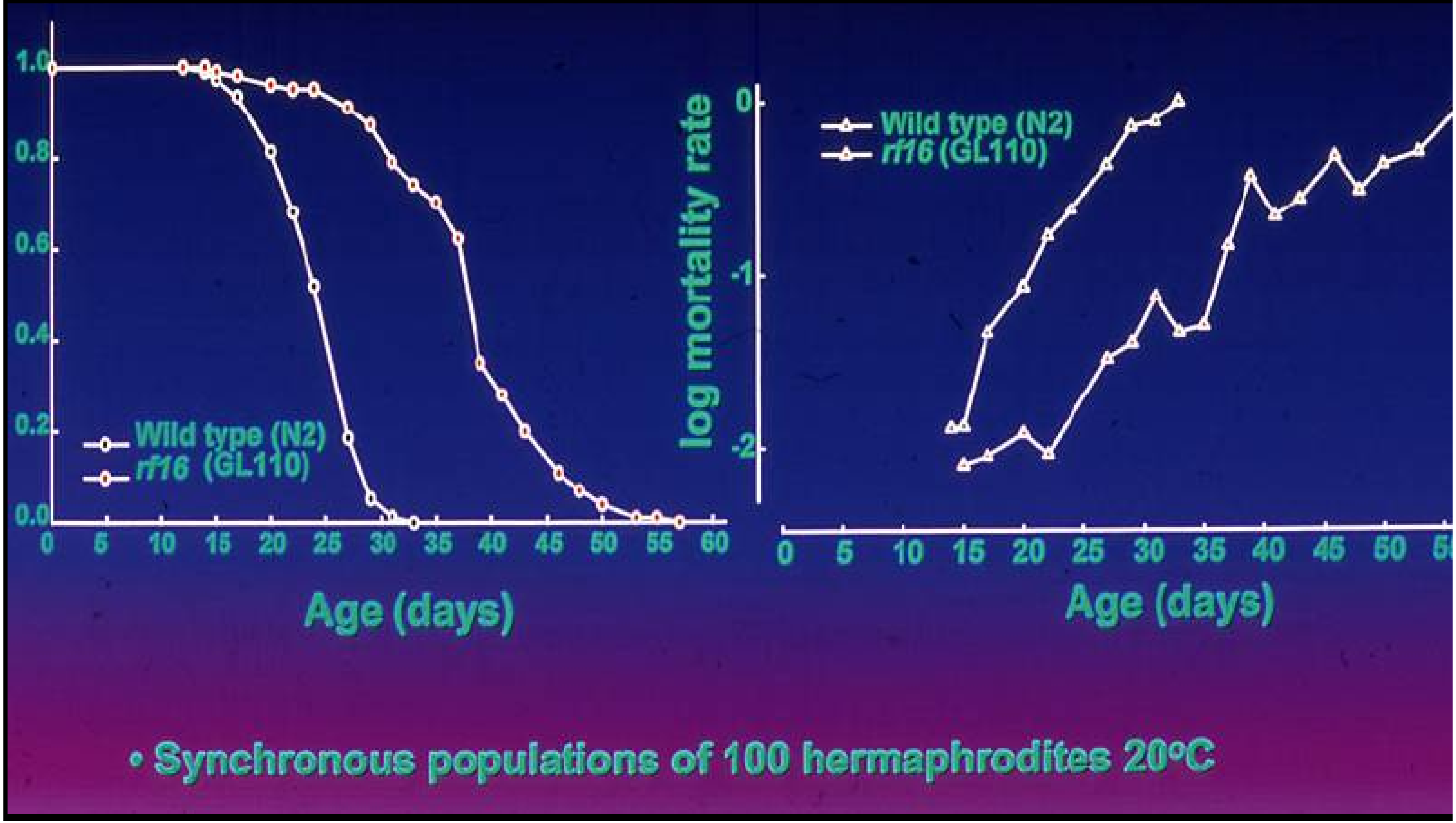
Centre for Integrated Systems Biology of Ageing and Nutrition
University of Newcastle upon Tyne



2nd FEBS Advanced Lecture Course

Systems Biology From Molecules to Life and Death!!

Single Gene Mutations Affect Nematode Life Span



Genetic Regulation of *C. elegans* Lifespan

daf-2 (IGF-1 homolog) mutations produce up to two-fold increases in lifespan

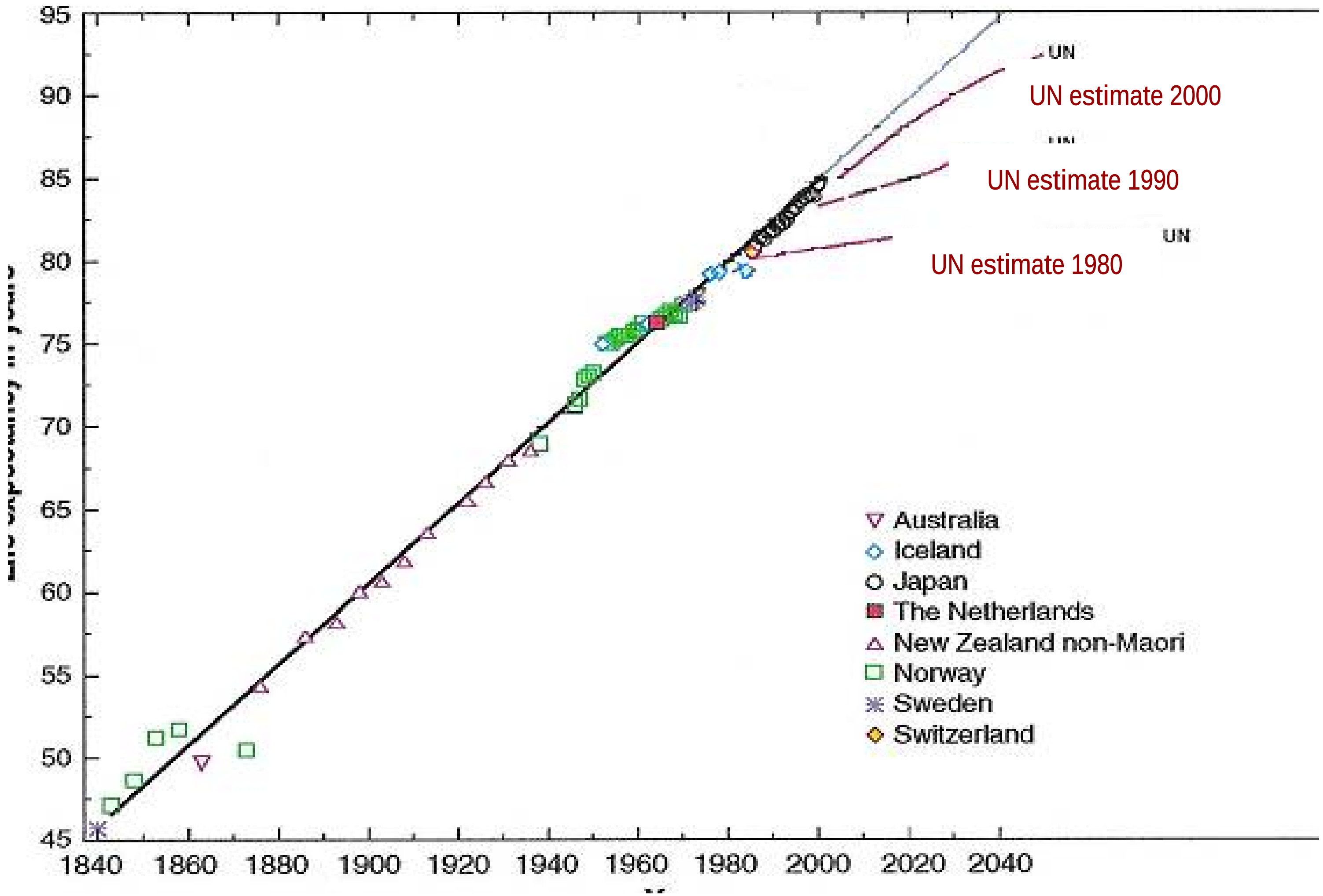
- These act via the influence of *daf-2* on *daf-16*
- Mutations in *daf-16* reduce lifespan of *daf-2* mutants back to wt

Murphy et al *Nature* 2003

- Microarray expression screens of RNAi-induced phenocopies of DAF-16 mutations used to identify downstream genes
  - 189 activated by DAF-16; 122 repressed

- Genes modulated by DAF-16 regulate:
  - Stress resistance
  - Antimicrobial resistance
  - Ubiquitin-mediated protein turnover

The Continuing Increase in Life Expectancy

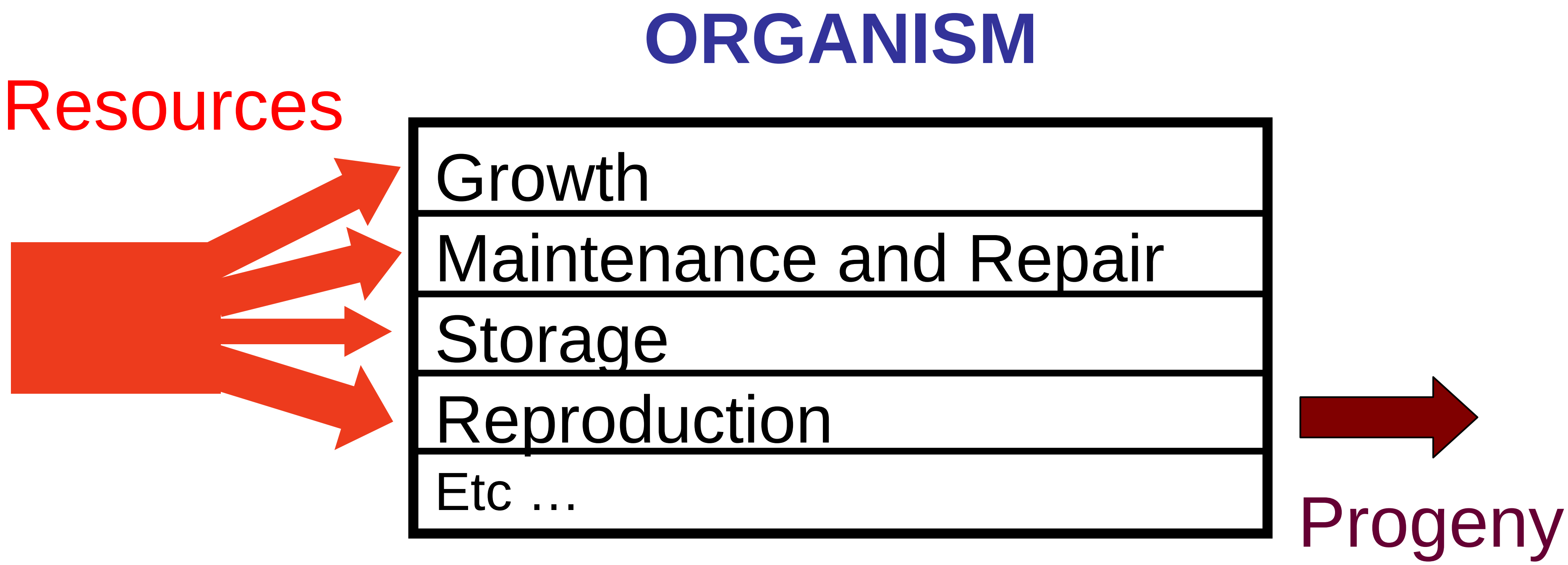


Life expectancy is increasing by 5 hours a day

Systems Biology of Ageing

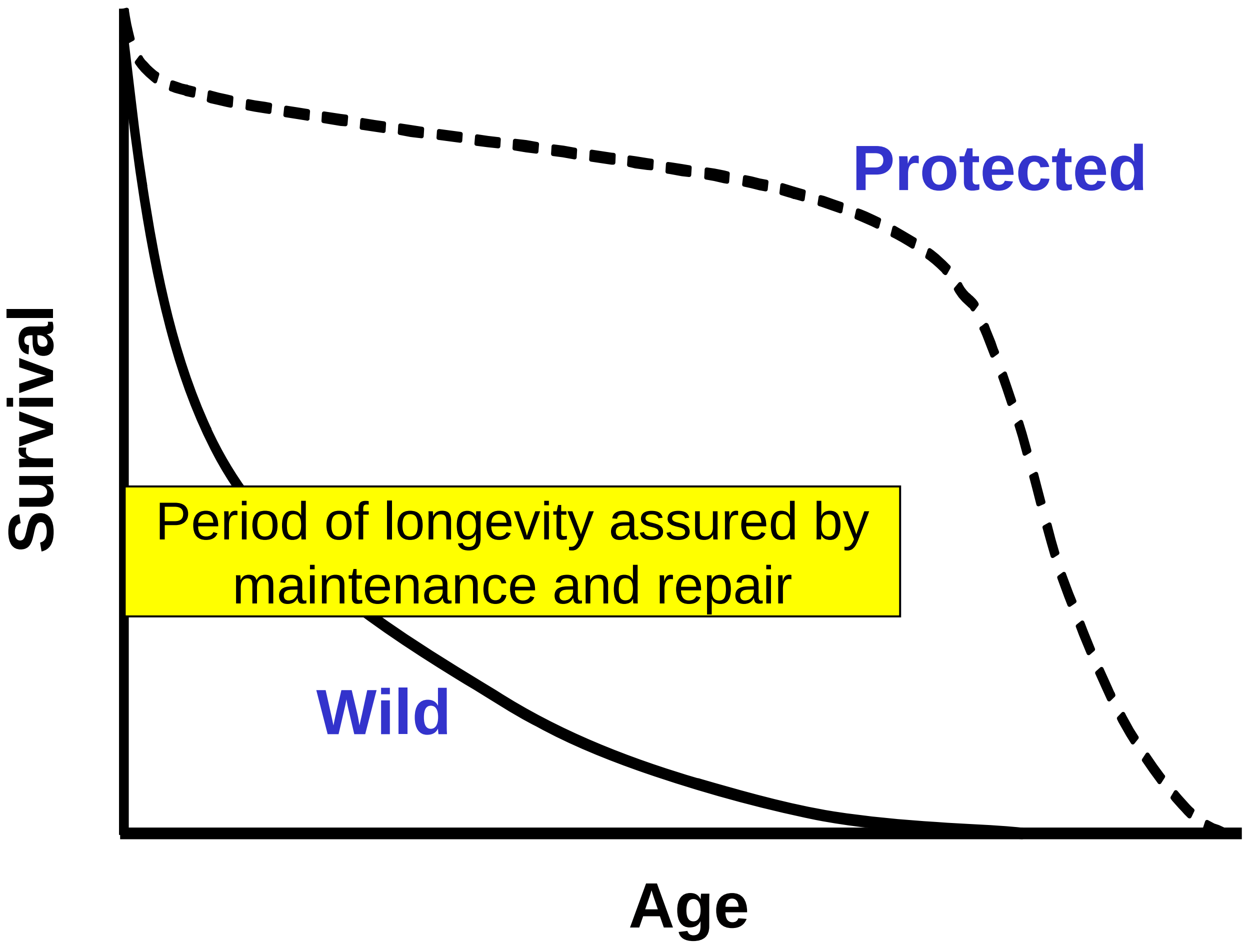
- Why do our bodies age?
- How do cells last so long?
- Failure of robustness?
- Where are the weak links?
- Can we slow the process down?

RESOURCE ALLOCATION AND FITNESS



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

DISPOSABLE SOMA THEORY



Kirkwood *Nature* 1977

Implications of the Disposable Soma Theory

- Ageing caused primarily by damage
- Longevity regulated by resistance/repair
- Enhanced resistance/repair in germ-line

- Multiple mechanisms; Complexity
- Inherently stochastic

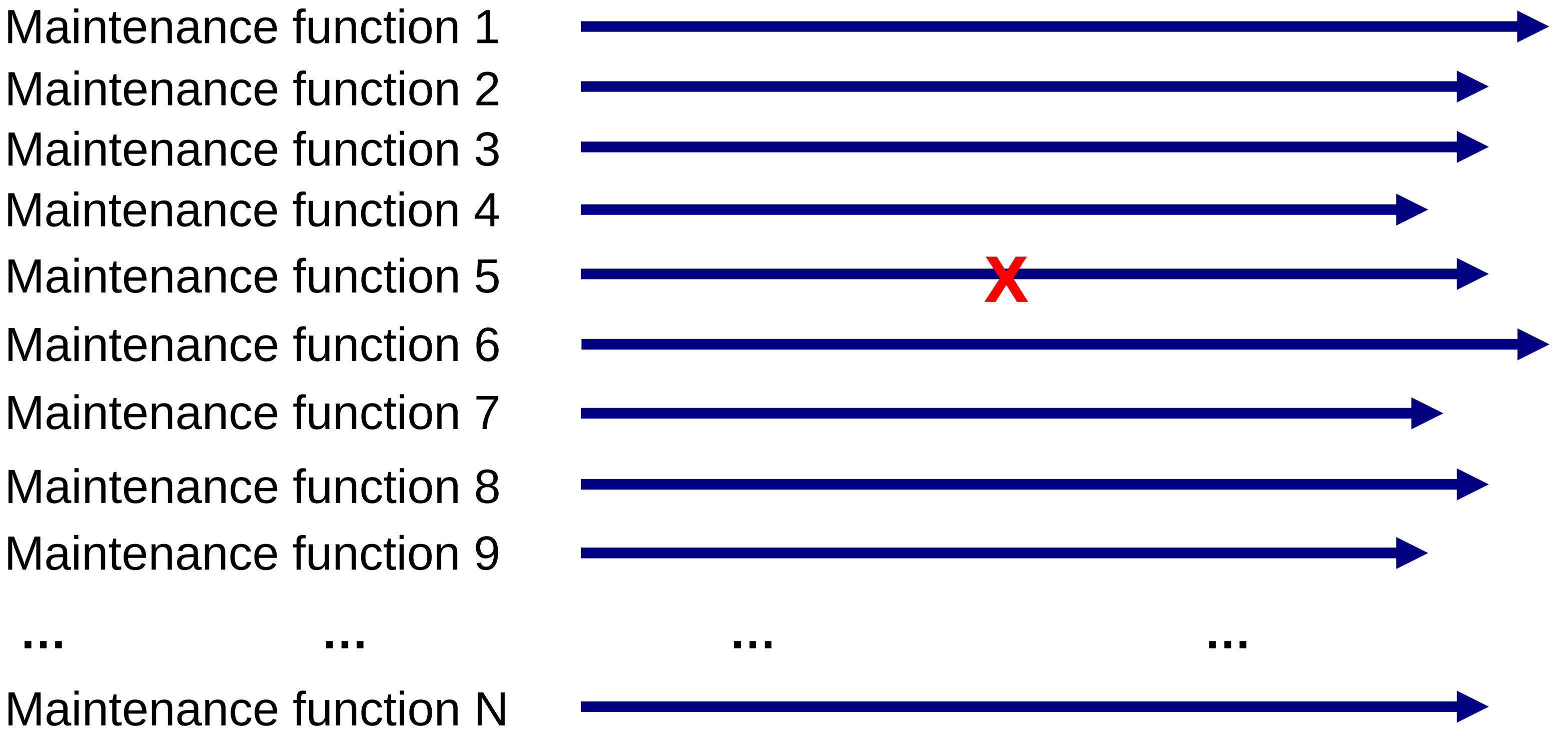
- Optimality; Plasticity; Trade-offs

GENETIC CONTROL OF LONGEVITY

Maintenance function 1
Maintenance function 2
Maintenance function 3
Maintenance function 4
Maintenance function 5
Maintenance function 6
Maintenance function 7
Maintenance function 8
Maintenance function 9
... ...
Maintenance function N

N = ??

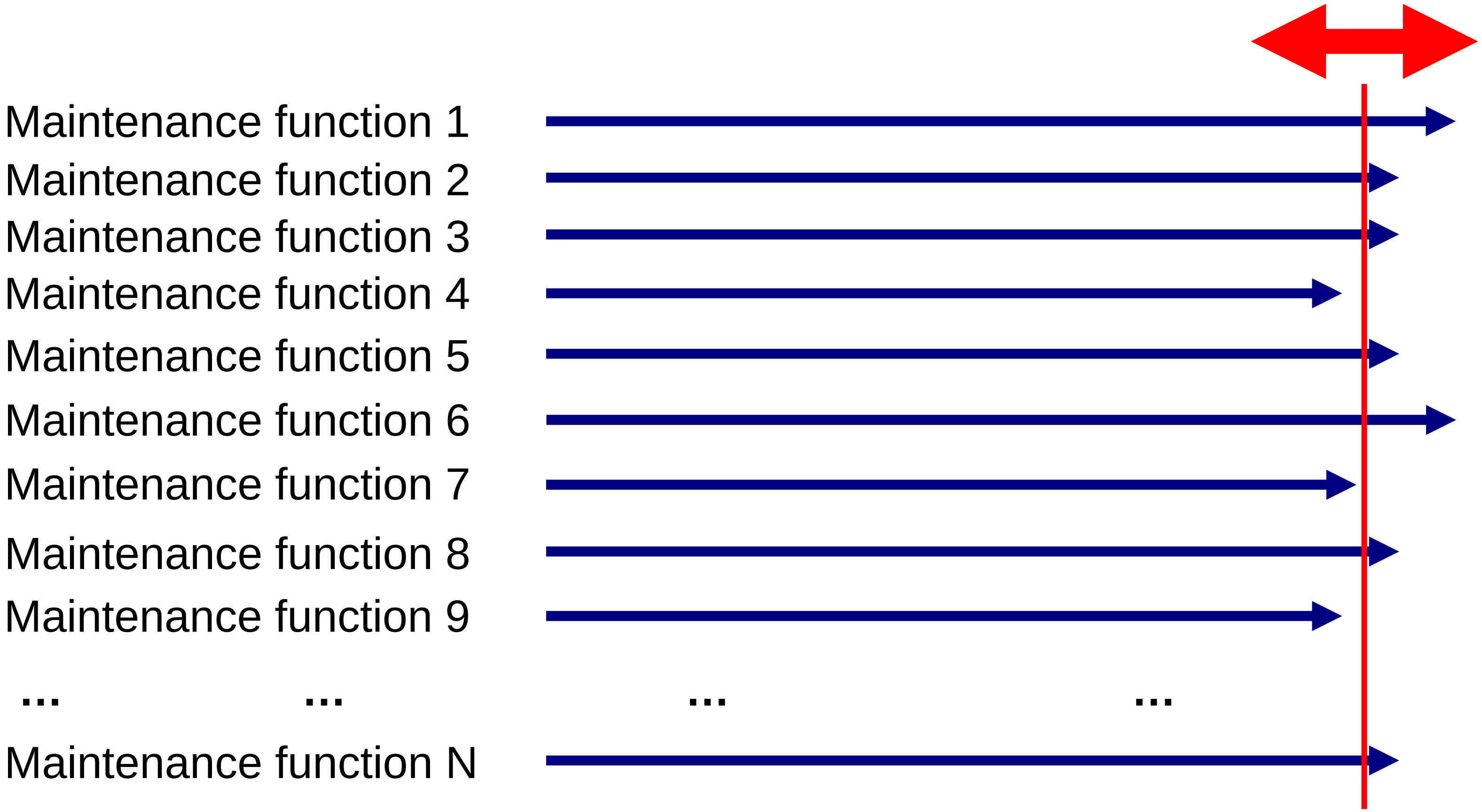
GENETIC MODELS OF ACCELERATED AGEING



Are the accumulated lesions similar in nature to those occurring during normal ageing?

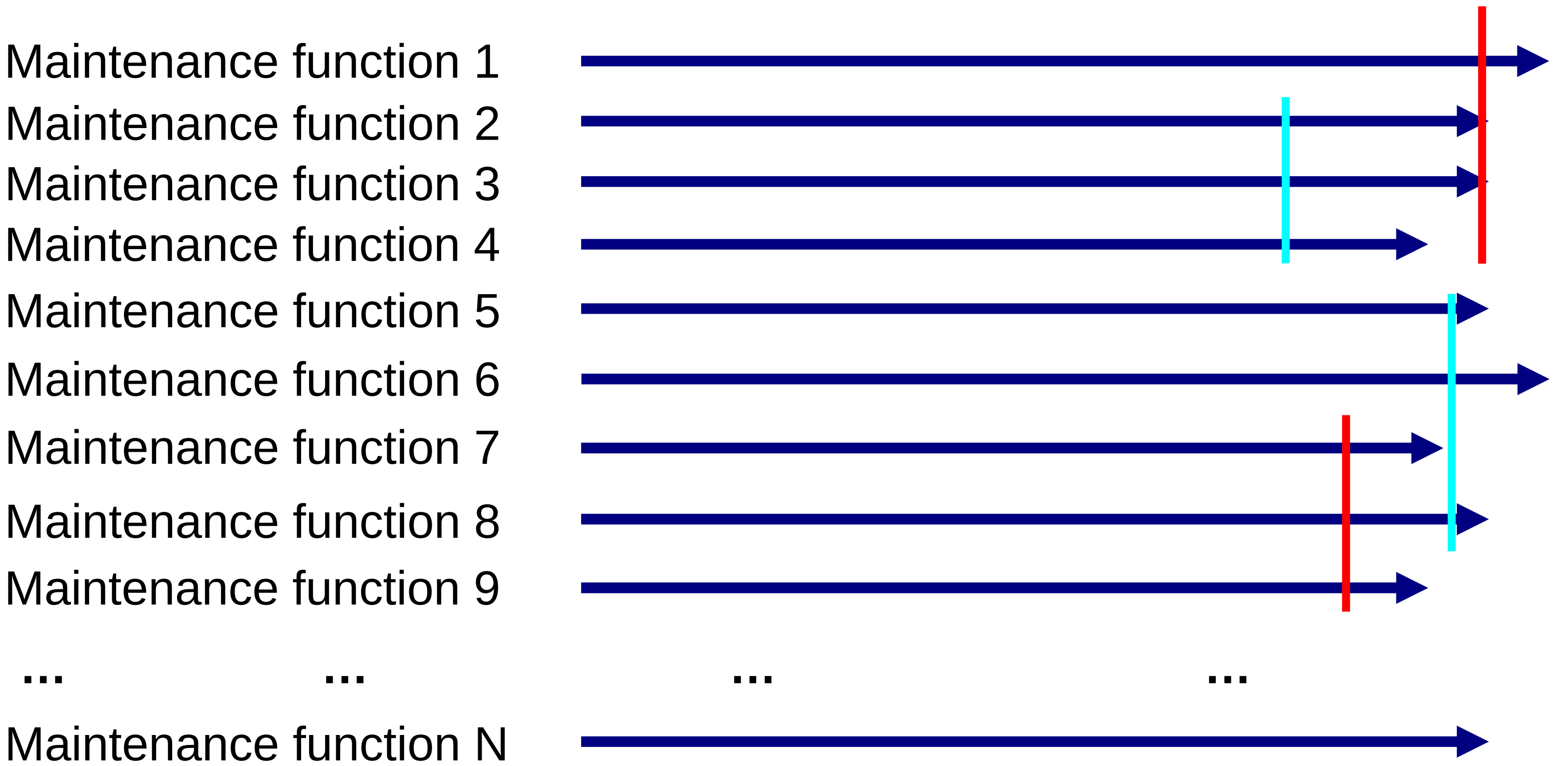
Might the model miss essential interactions which would otherwise occur with other lesions contributing to normal

GENE REGULATORY ARCHITECTURE



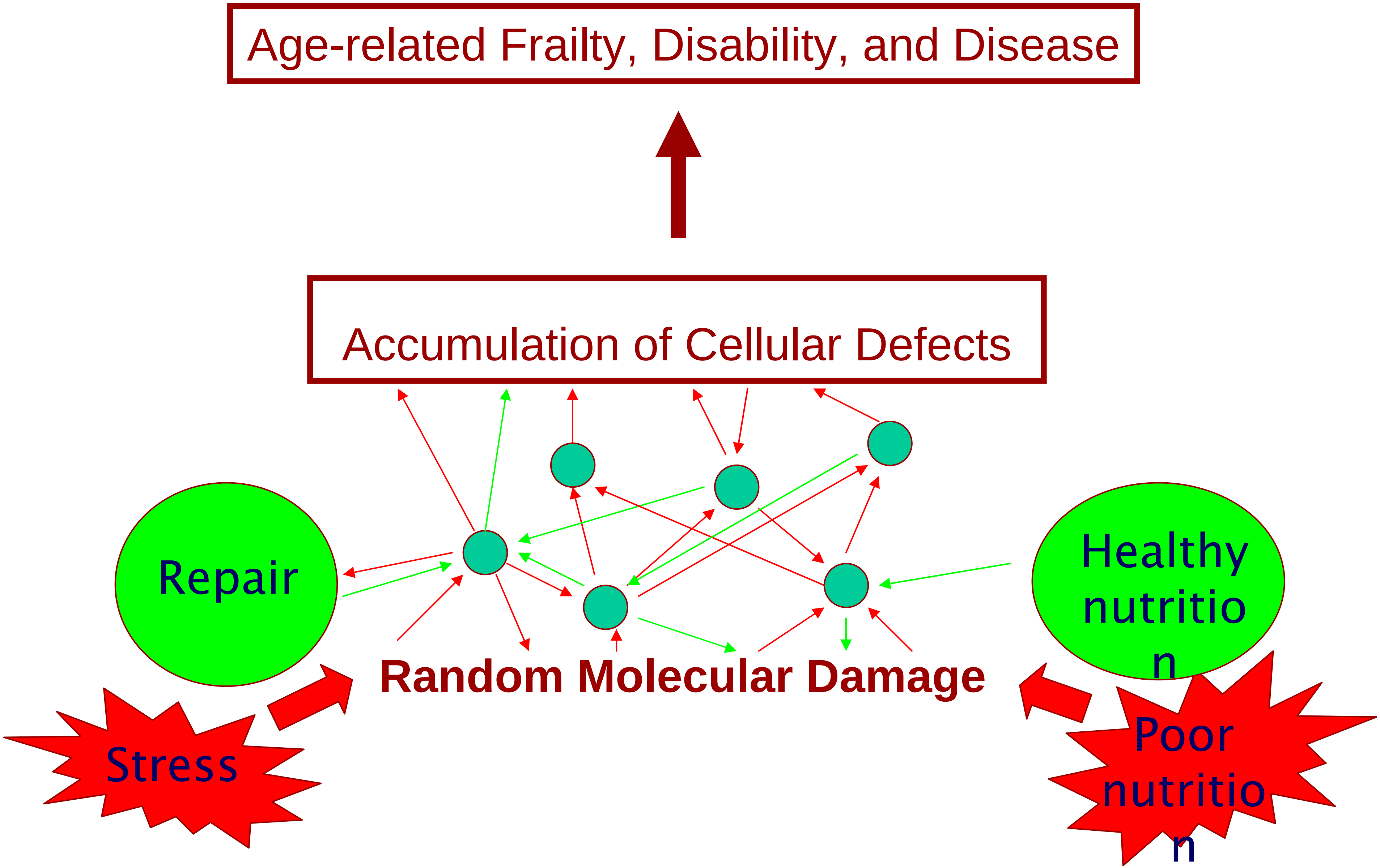
- **Regulatory genes may respond to nutrient levels, temperature, population density, etc.**
- **Species requirement to evolve regulation will depend on ecology**

TISSUE-SPECIFIC GENE REGULATION

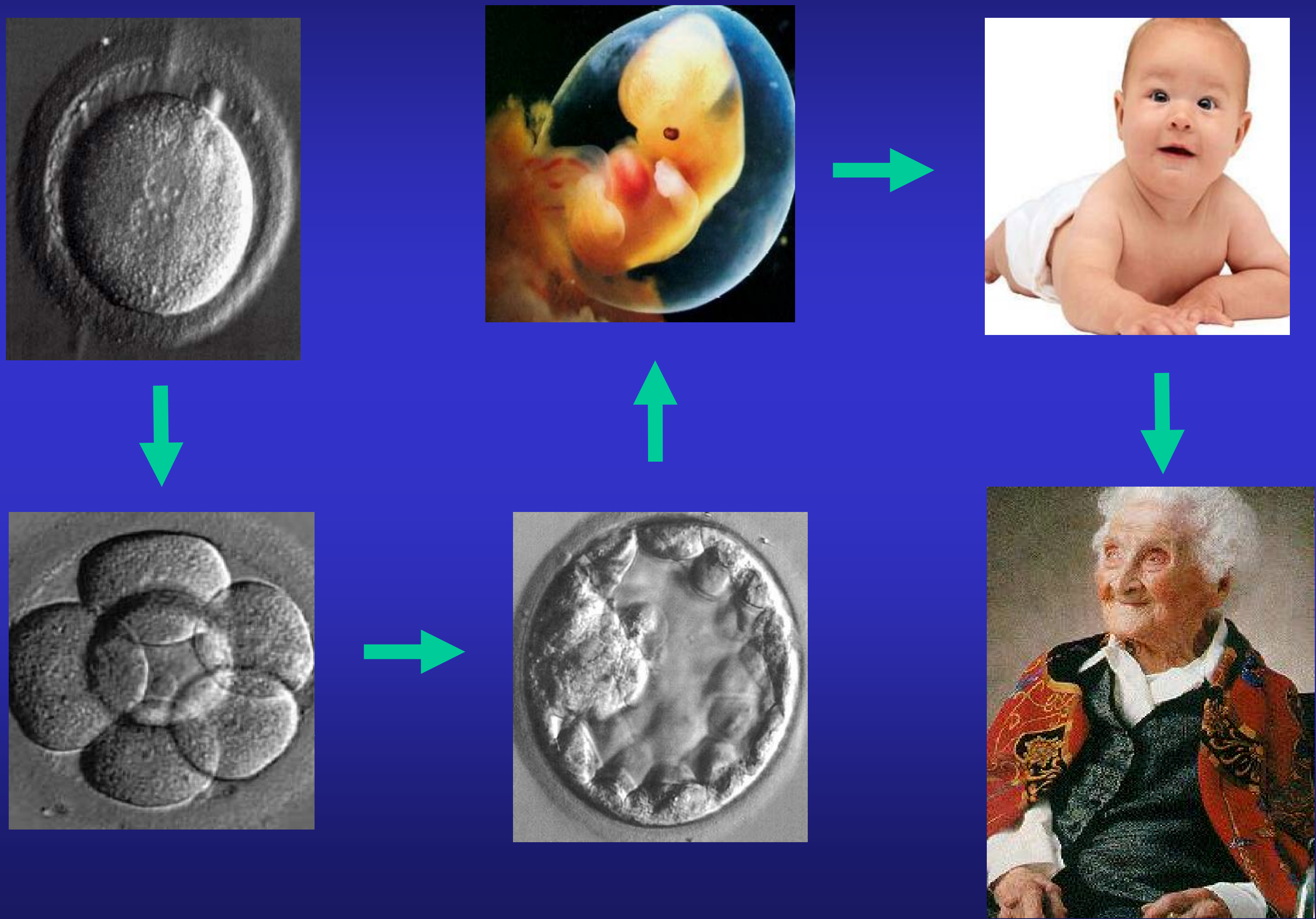


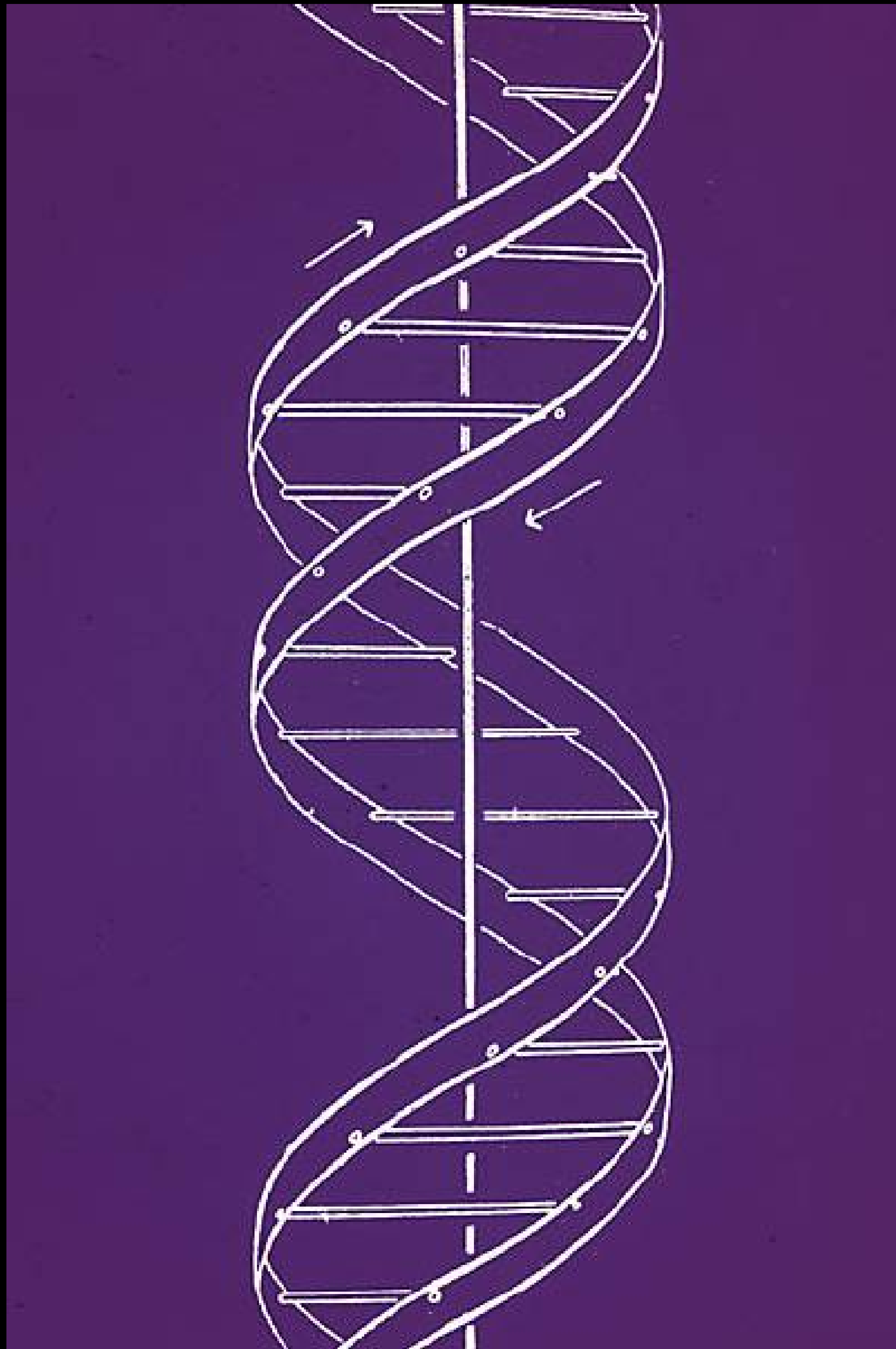
Different cell types have different vulnerability to particular kinds of damage

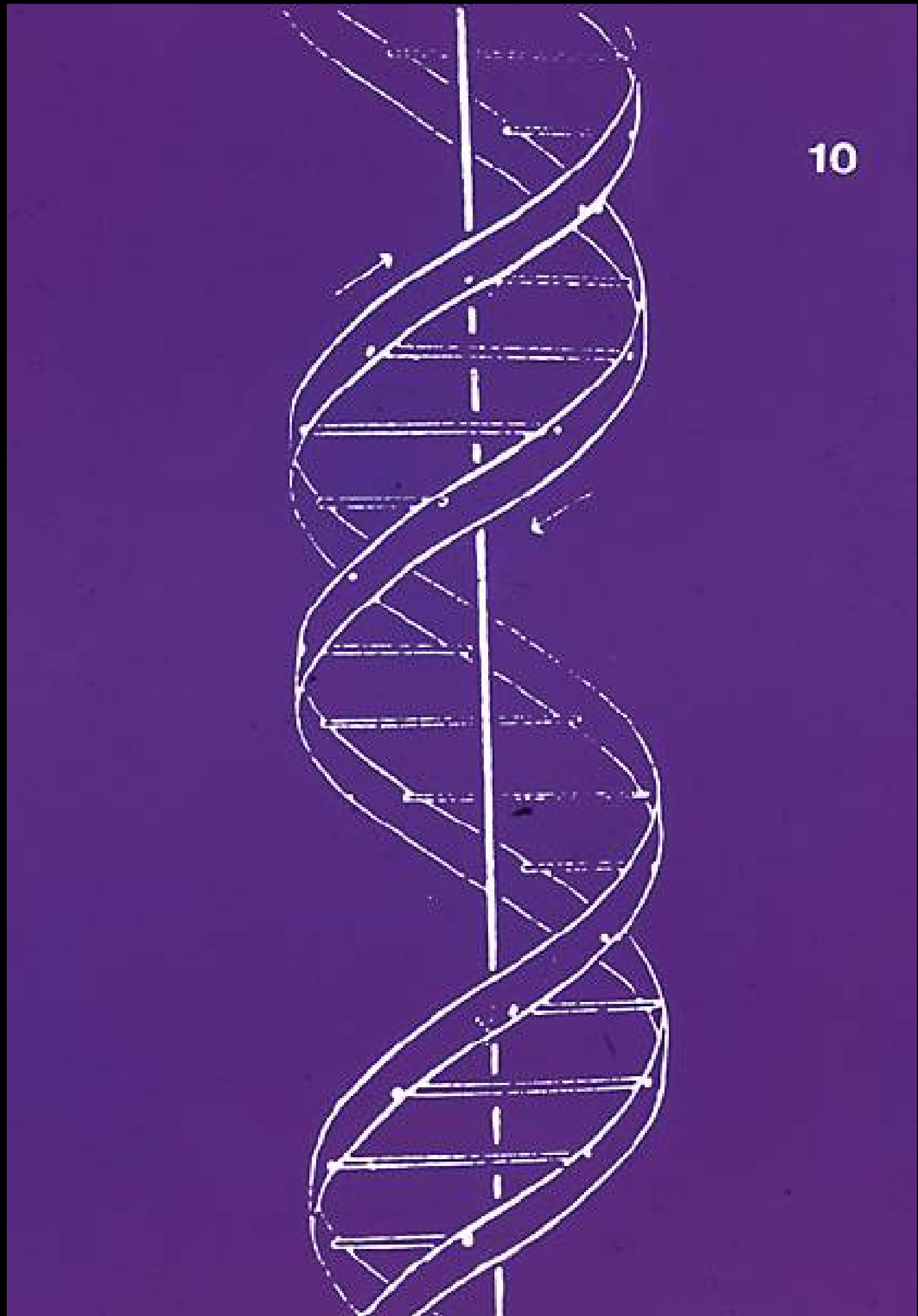
The Ageing Process



From One Cell to 100 Million Million



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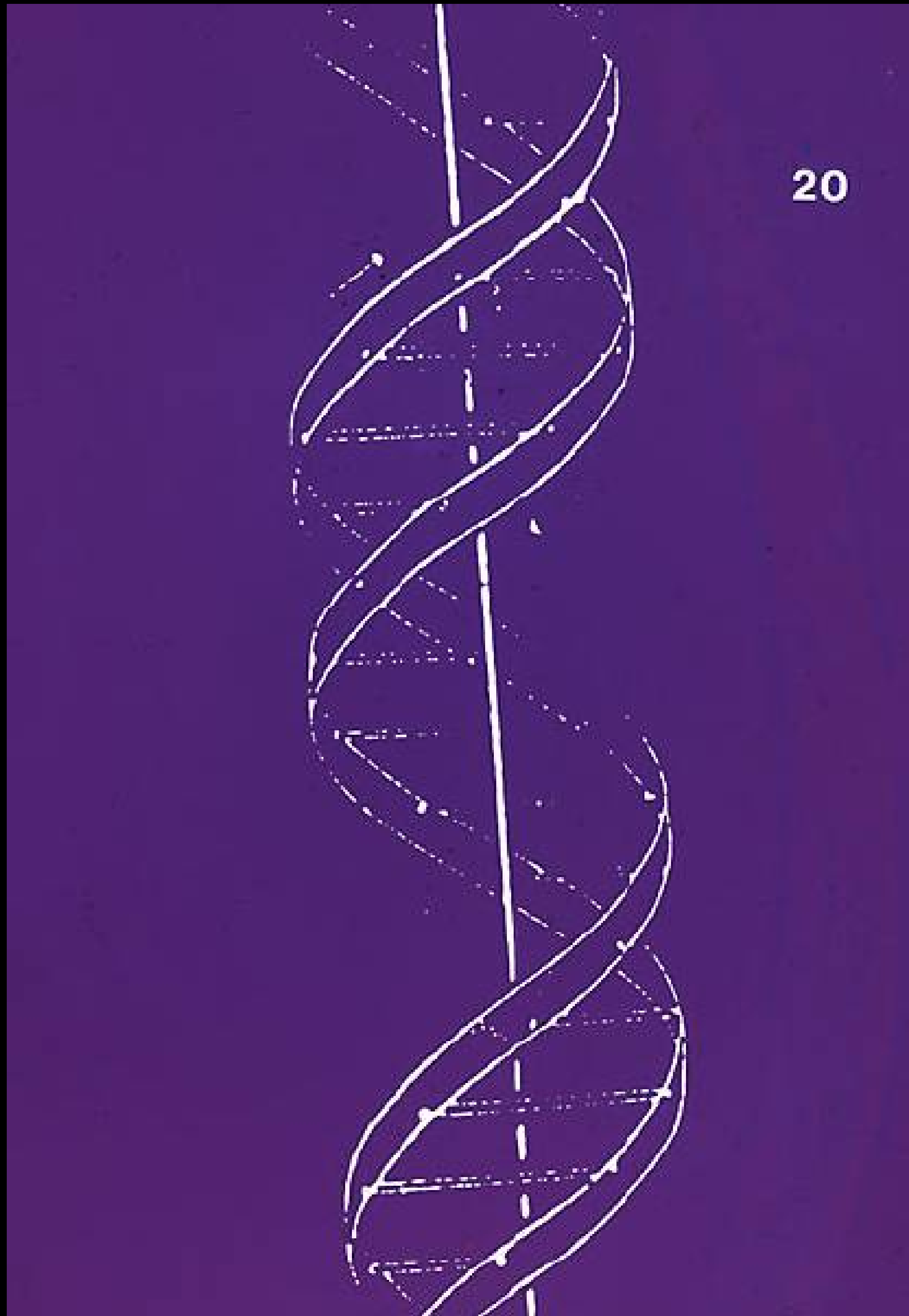
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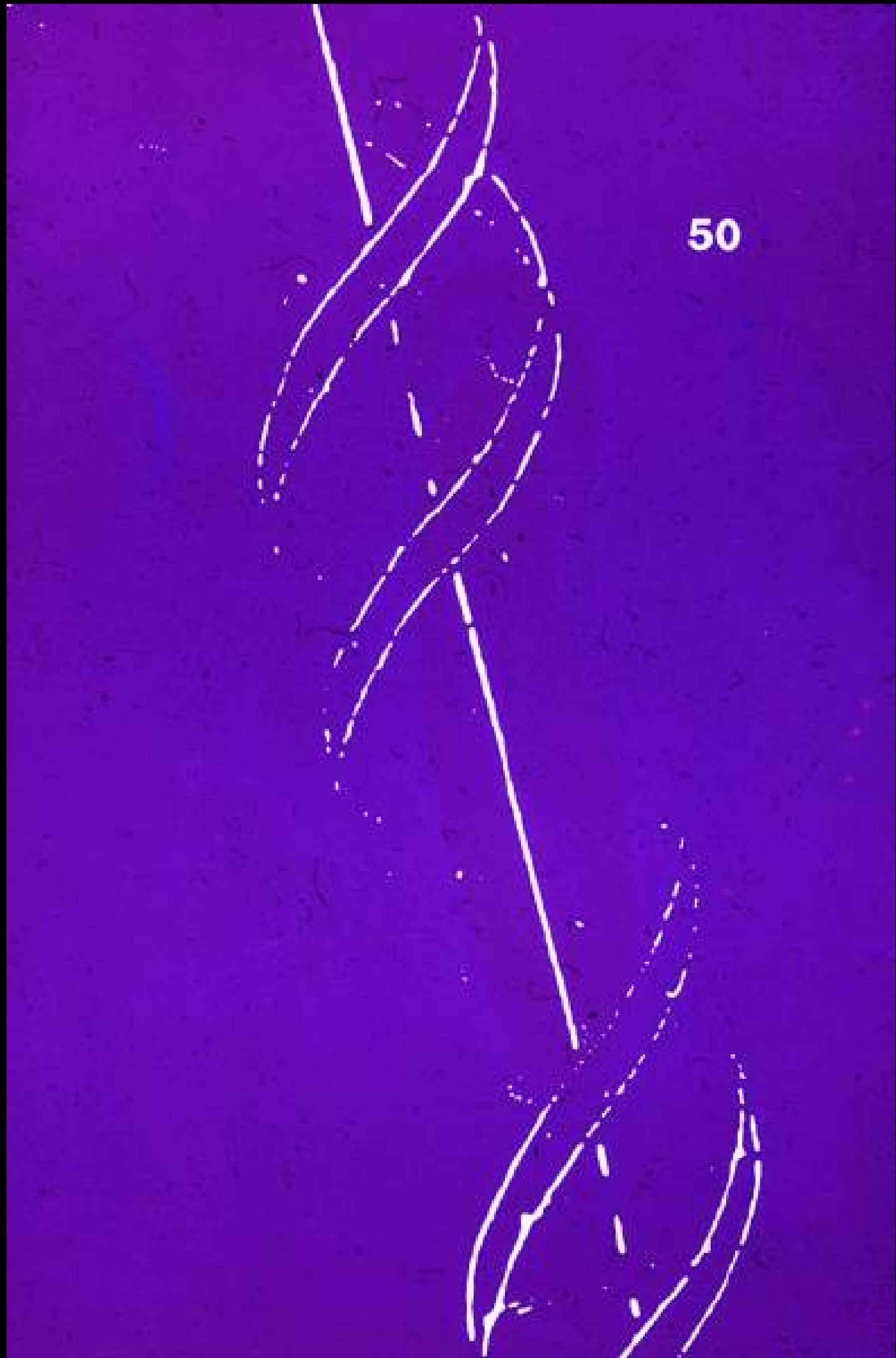
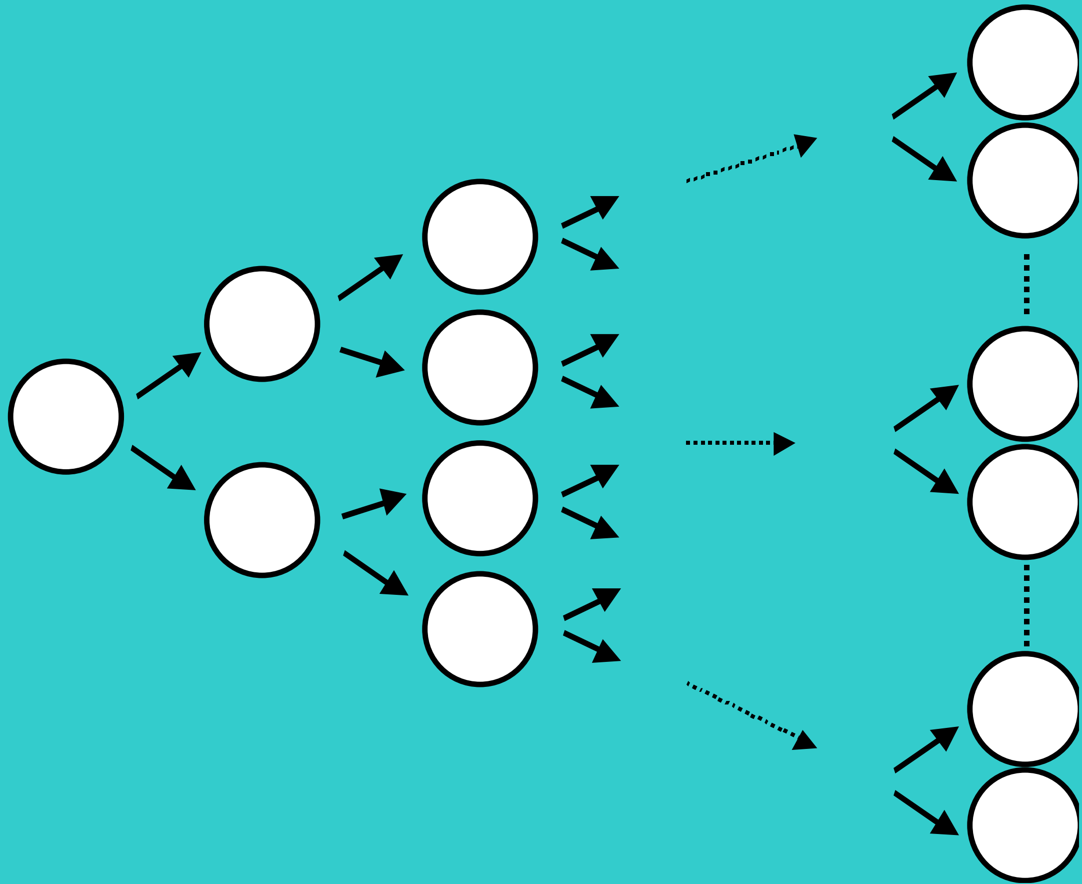
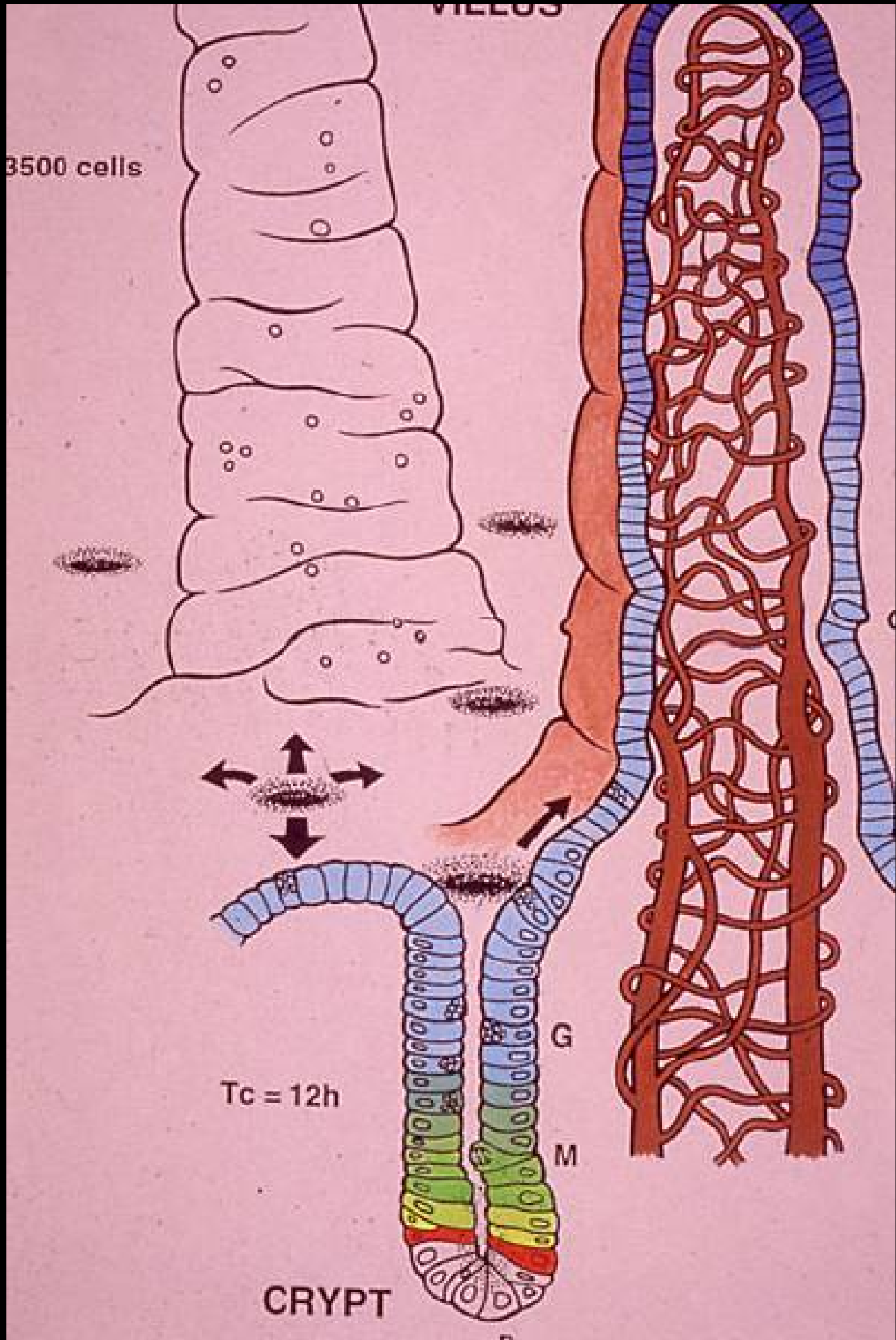

50

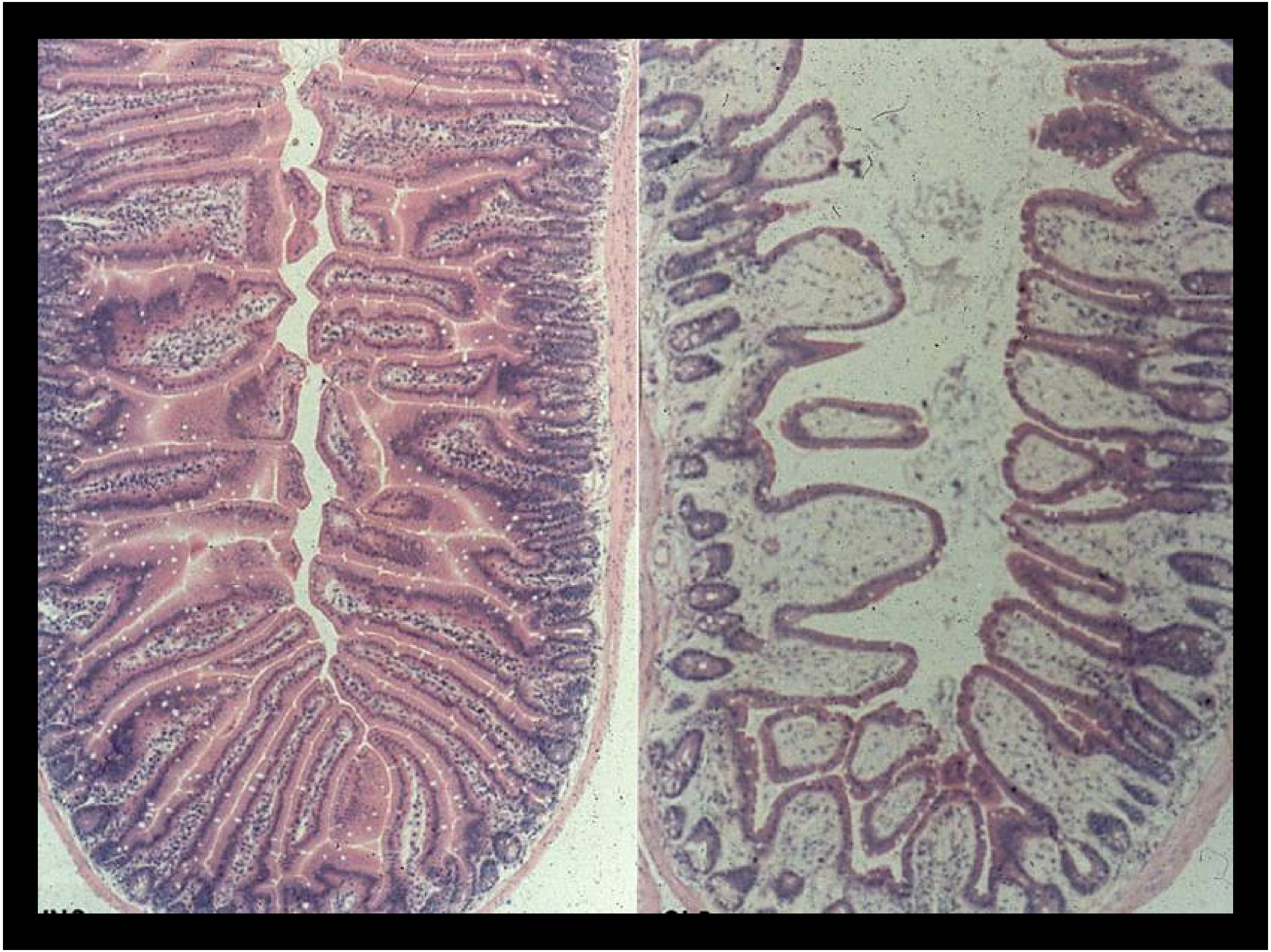
Cell Multiplication and Somatic Mutation



Number of cells:	**1**	**2**	**4**	**…**	**…**	**10^{14}**
Cell generation:	**0**	**1**	**2**	**…**	**…**	**46**
Mutations per cell:	**0**	**6**	**12**	**…**	**…**	**276**



VILLUS
3500 cells
G
Tc = 12h
M
CRYPT



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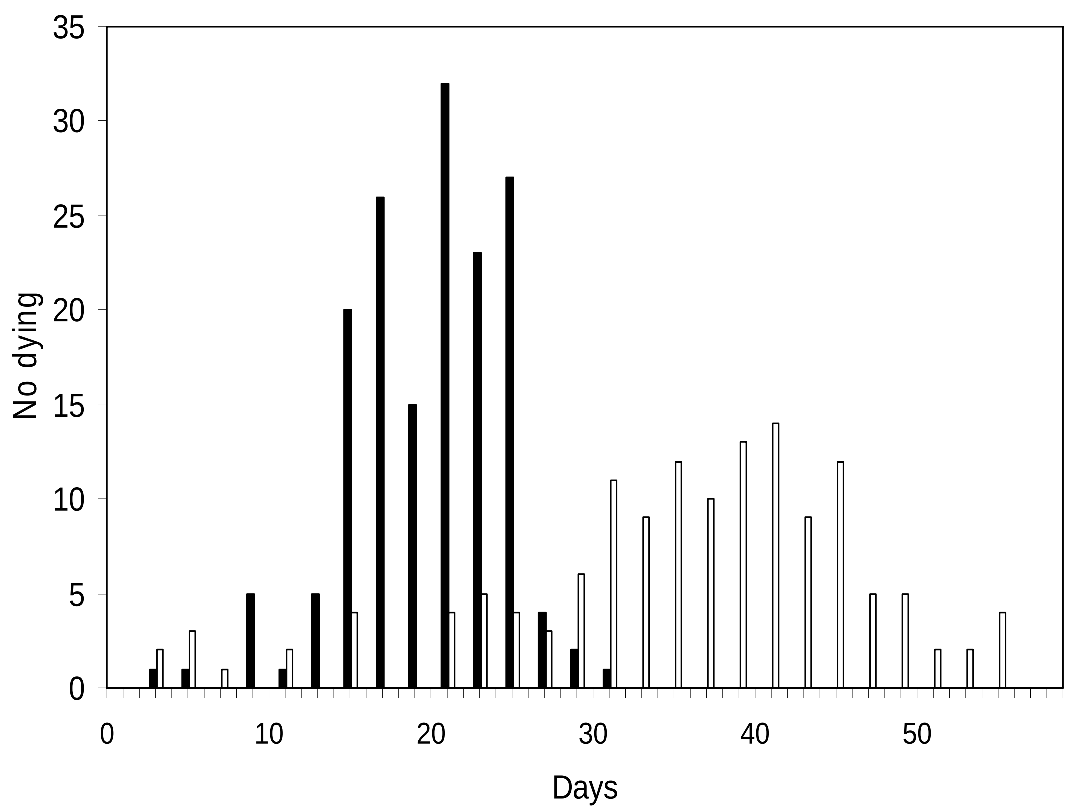
Ages at Death of Wild-type and *age-1* Worms

Kirkwood & Finch *Nature* 2002 (redrawn from Johnson 1990)



tochastic and genetic factors nfluence tissue-specific decline n ageing *C. elegans*

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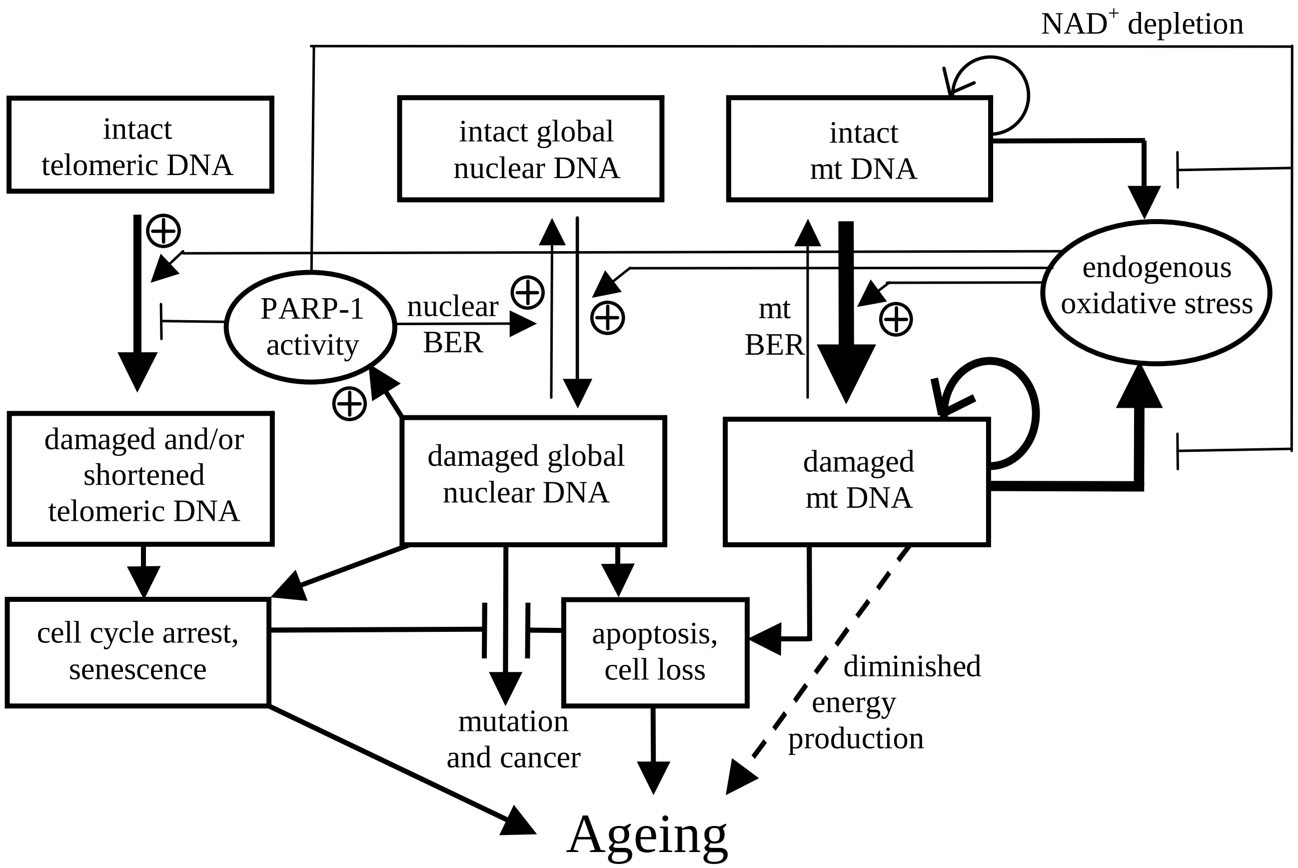
nematode *Caenorhabditis elegans* is an important model for studying the genetics of ageing, with over 50 life-exte tions known so far. However, little is known about the pathobiology of ageing in this species, limiting attempts to co type with senescent phenotype. Using ultrastructural analysis and visualization of specific cell types with green fluore ein, we examined cell integrity in different tissues as the animal ages. We report remarkable preservation of the ne em, even in advanced old age, in contrast to a gradual, progressive deterioration of muscle, resembling human sarcopeni *1(hx546)* mutation, which extends lifespan by 60–100%, delayed some, but not all, cellular biomarkers of ageing. Striki ound strong evidence that stochastic as well as genetic factors are significant in *C. elegans* ageing, with extensive varia

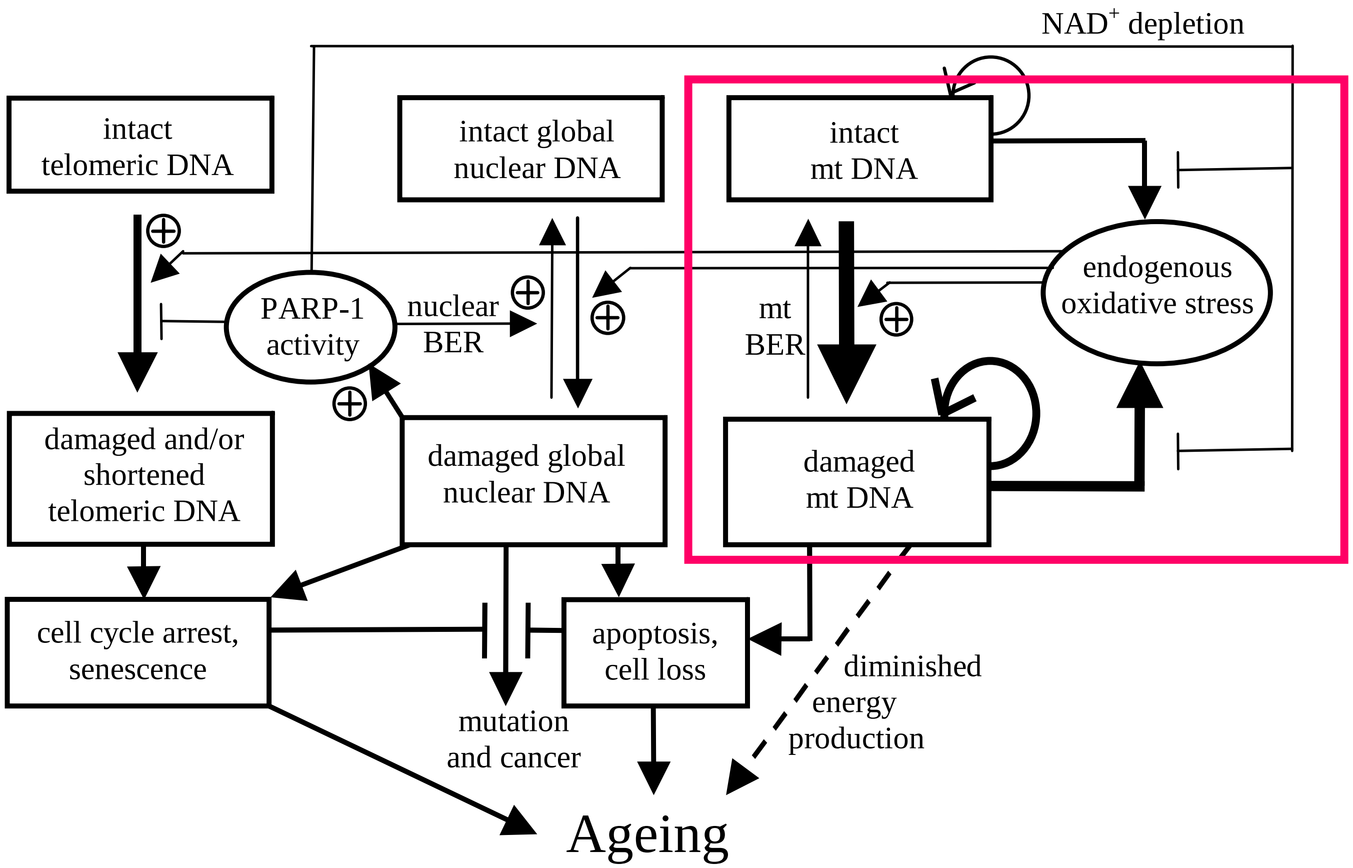
Herndon et al *Nature* 2002

OXIDATIVE STRESS AND DNA DAMAGE

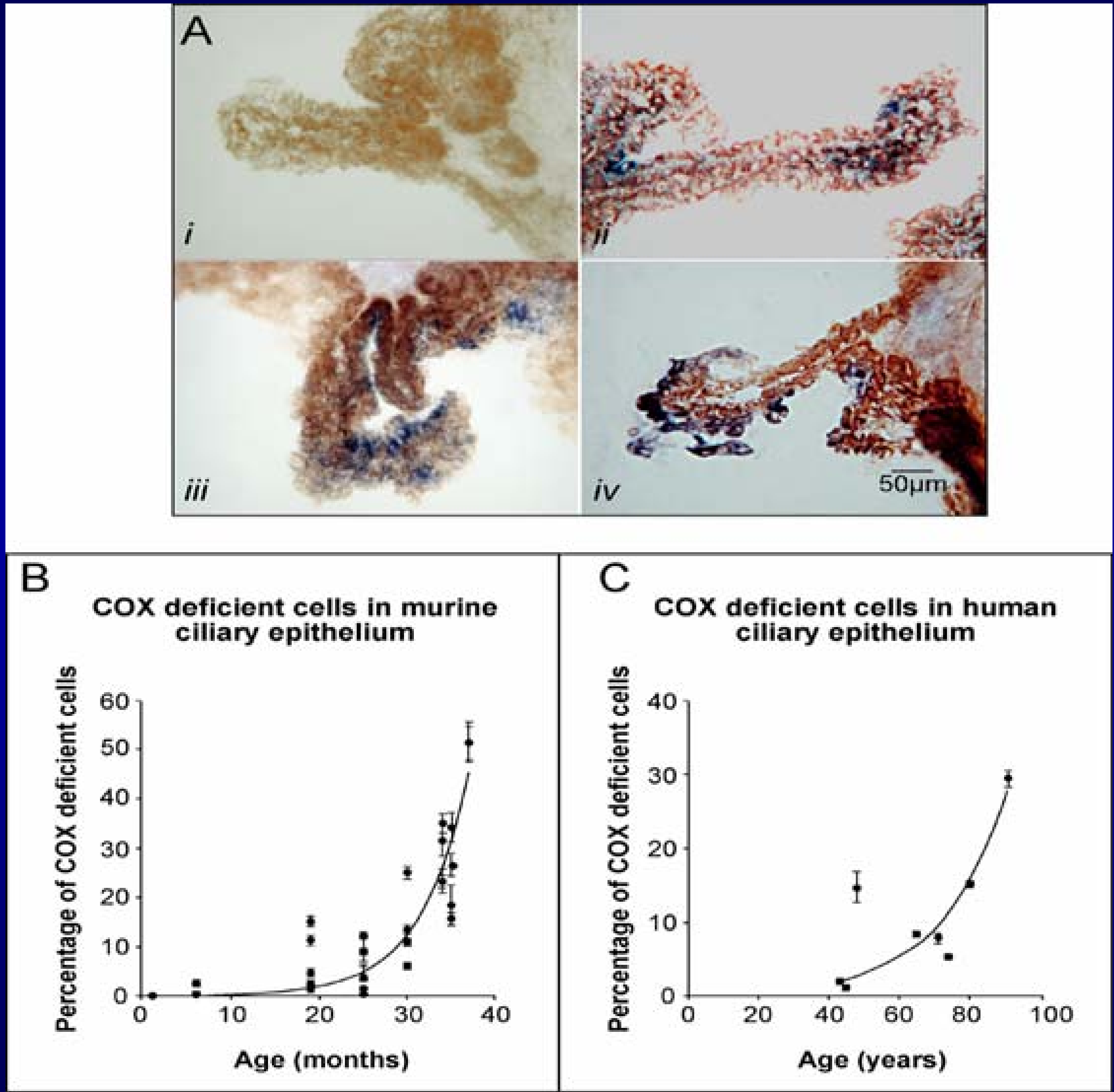


von Zglinicki, Bürkle, Kirkwood Exp Gerontol 2001

OXIDATIVE STRESS AND DNA DAMAGE

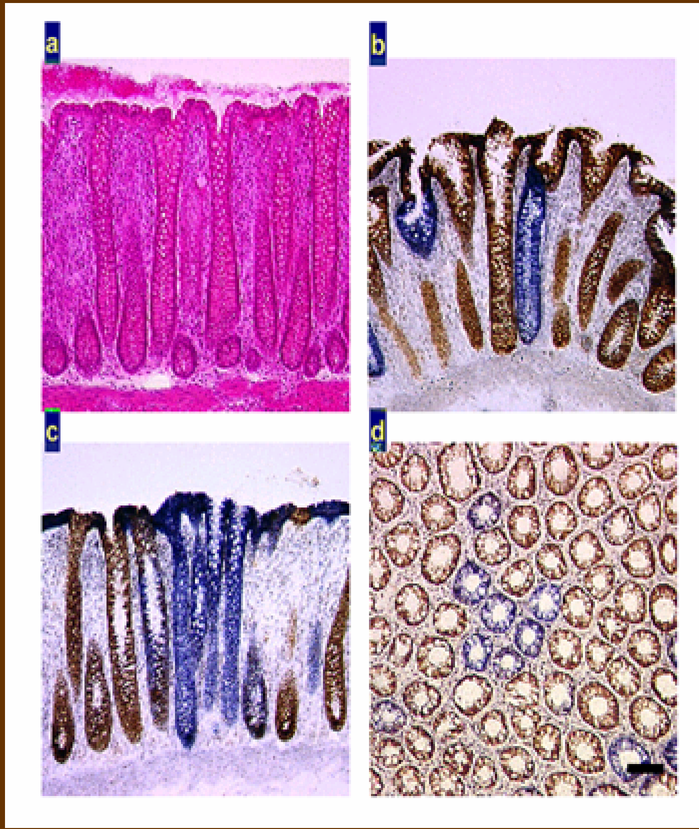


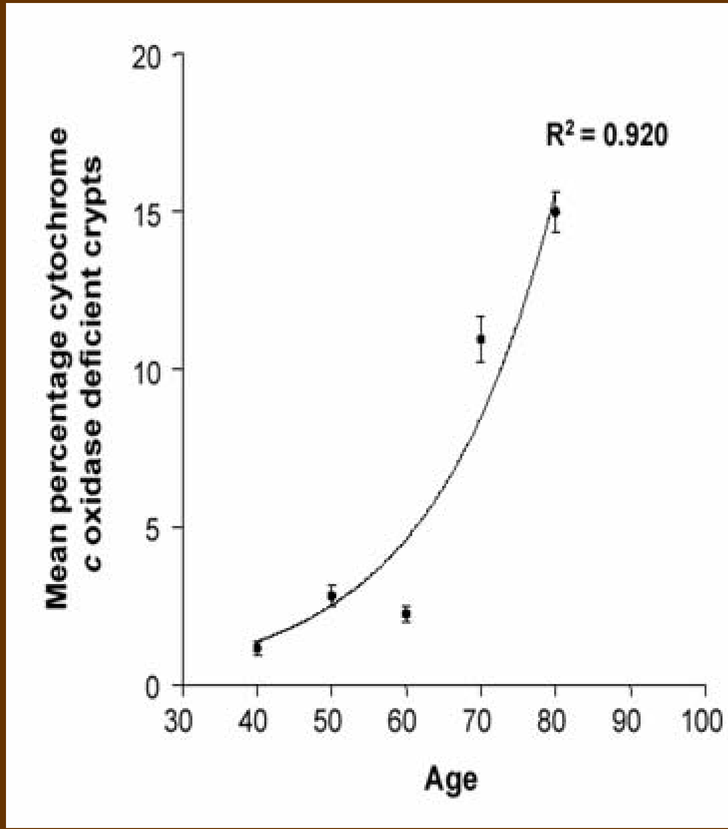
Mitochondrial Mutations in the Eye (Ciliary Epithelium)



Barron, Kirkwood, Clarke, Turnbull, *unpublished*

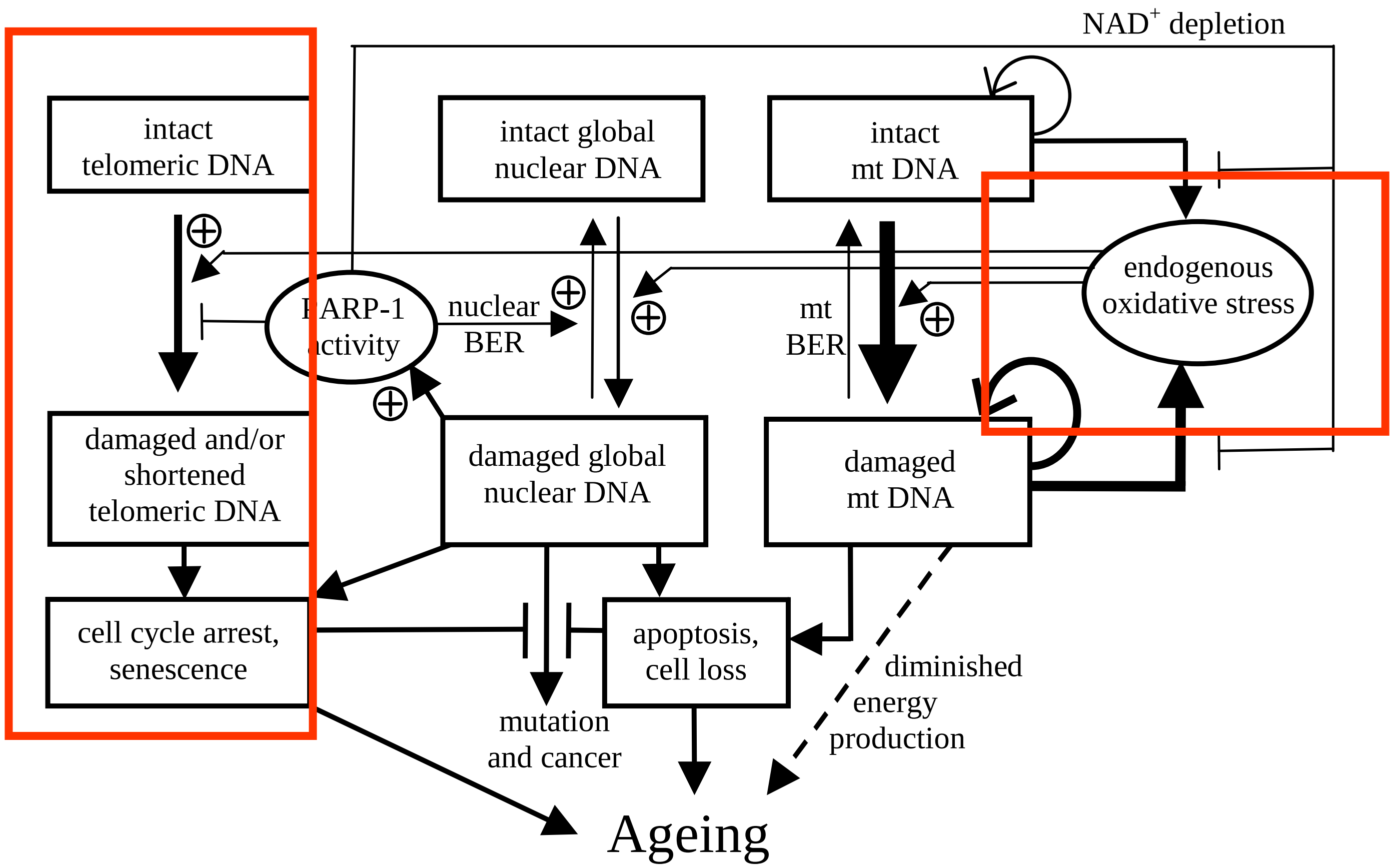
Mitochondrial Mutations in Ageing Tissue



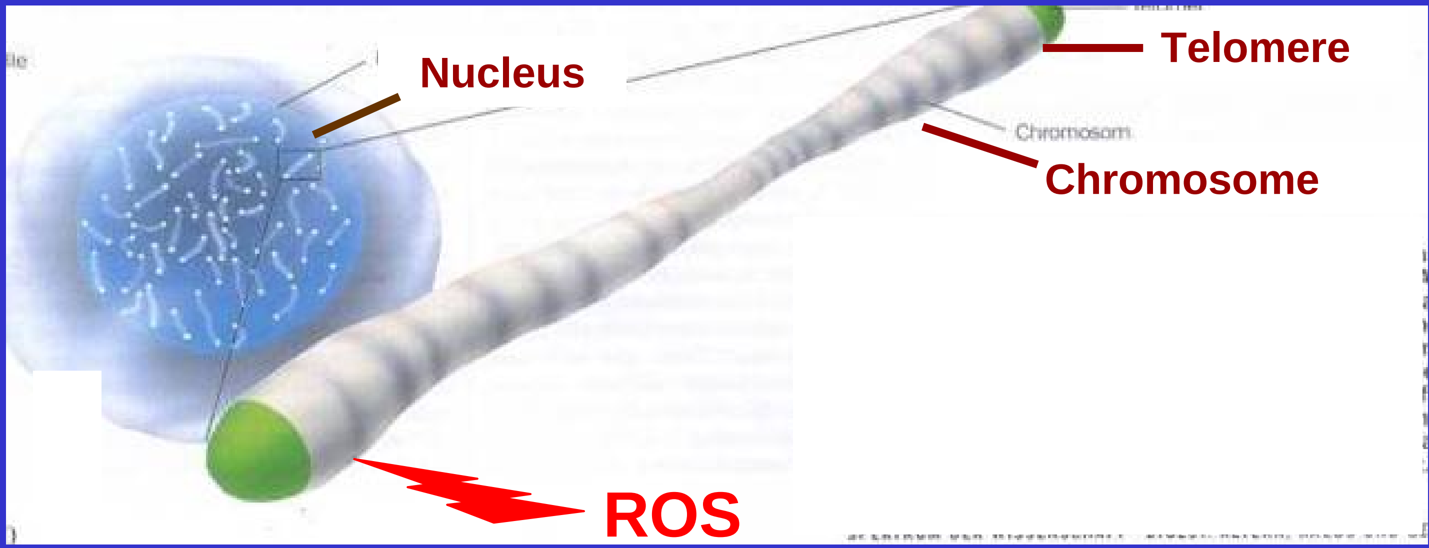


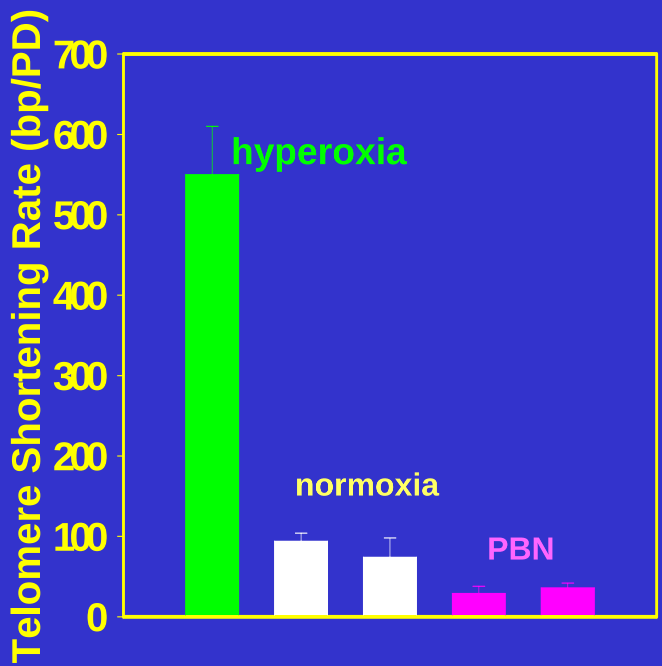
Taylor et al *J Clin Invest* 2003

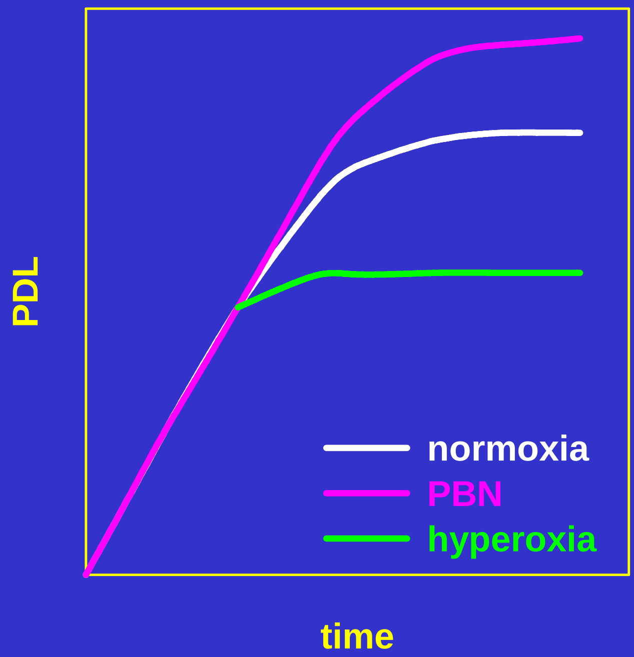
OXIDATIVE STRESS AND DNA DAMAGE



Stress Influences Telomere Shortening and Cell Senescence

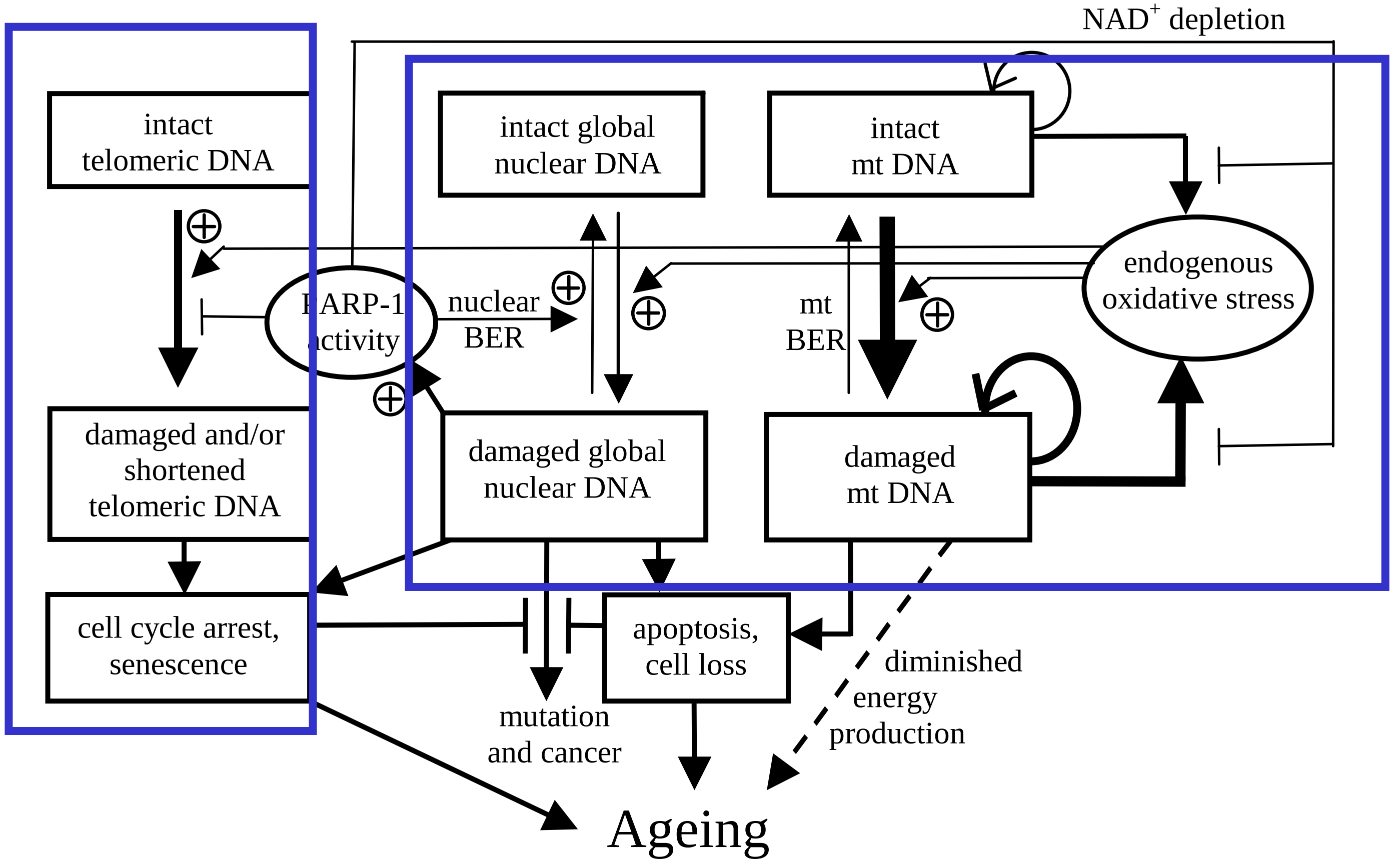






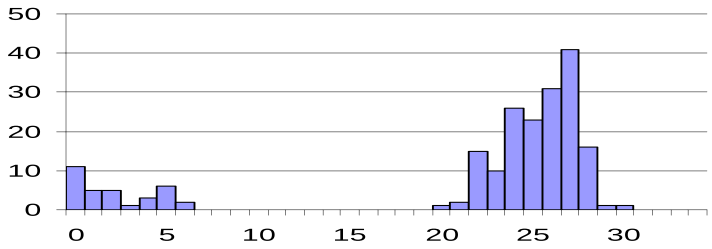
von Zglinicki et al. *Exp Cell Res* 1995; von Zglinicki et al. *FRBM* 2000

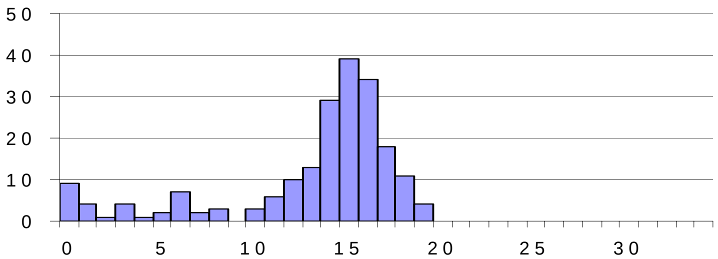
OXIDATIVE STRESS AND DNA DAMAGE

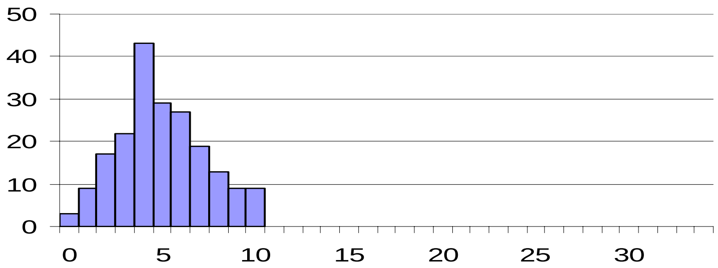


Variation in Cell Doubling Potential

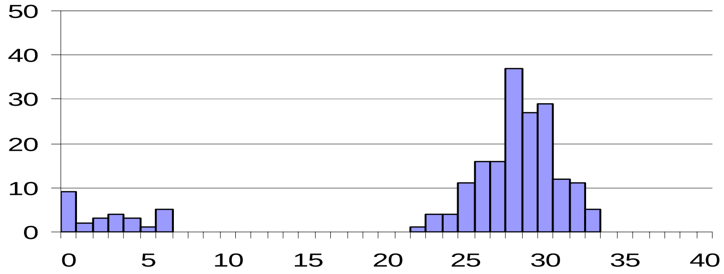
Observed (Smith & Whitney)

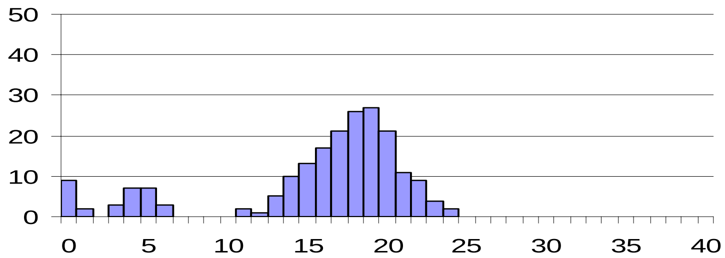


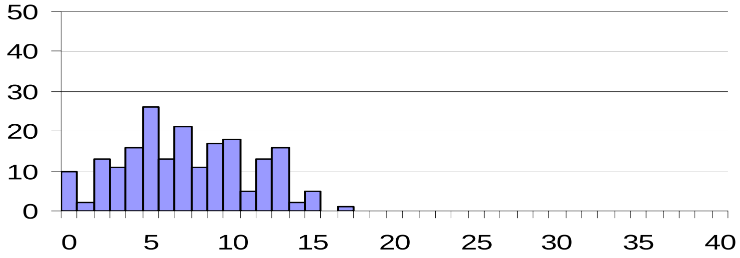




Predicted (Sozou & Kirkwood)*

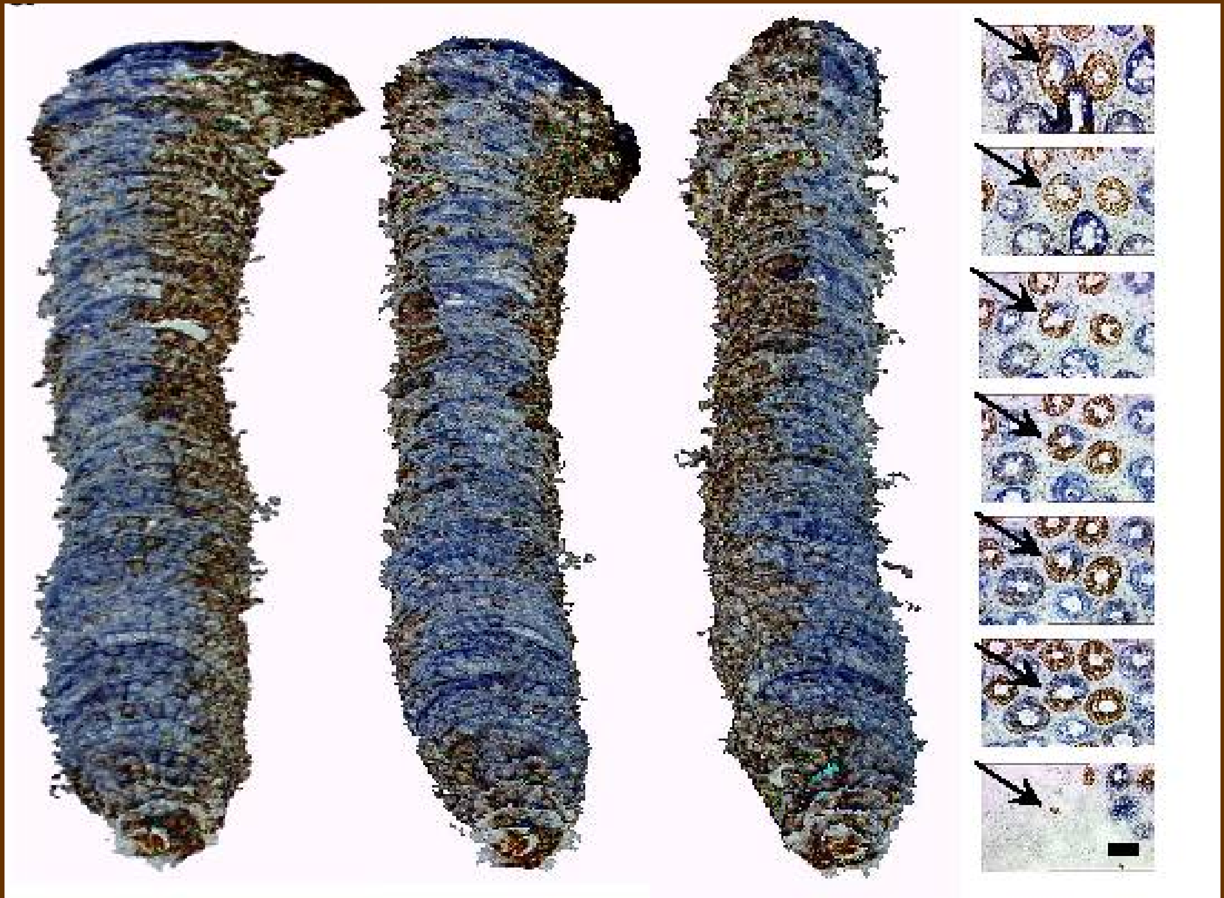






*Model incorporates oxidative stress, mitochondrial mutation, nuclear mutation, telomere erosion, and their interactions

Complex Questions About MtDNA Mutations



Taylor et al *J Clin Invest* 2003

Mitochondrial Mutations and Ageing?

- What causes mutations (stress, replication?)
- Spectrum of mutations (point vs deletion) and tissue specificity. Why?
- Clonal expansion of mutant mtDNA within cells.
  Driven or random?
- Functional consequences of mtDNA mutations within different tissues.
  - How do gut stem cells tolerate apparent high levels of mtDNA mutation?
  - Do mtDNA mutations drive tissue bioenergetic decline?
  - Are cells with mtDNA mutations more susceptible to apoptosis?
- Relationship between mtDNA mutation accumulation in age-related diseases (e.g. Parkinson's disease) and normal ageing?

Modelling ⟺ Experiment

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Optimising Cell Death

- Balance between cell survival and cell death
  - Deleting damaged cells protects against cancer
  - Excess cell death leads to loss of cellularity and accelerated ageing

- Tyner et al *Nature* 2002: p53 mutant mice that display:
  - Enhanced p53 activity
  - Reduced cancer incidence
  - Early ageing-associated pathology associated with reduced cellularity

CISBAN Experimental Programmes

- Network of mechanisms contributing to cellular ageing *in vitro*.
  - Telomere erosion.
  - Mitochondrial dysfunction.
  - Oxidative stress.
  - Protein homeostasis.

- How cell defects contribute to ageing *in vivo* (mouse model).
  - Nutritional interventions.
  - Biomarkers.
  - Lifespan.
  - Pathology.
  - Heterogeneity.

- Yeast as a model for high throughput screening of genes involved in damage responses, and their susceptibility to nutrition.

CISBAN *in silico* Components

- Data management and integration
  - Bioinformatics Support Unit and Regional e-Science Centre
  - Semantic data integration tools (based on Comparagrid)
  - Workflow tools (based on myGrid and others)

- Modelling tools and environment
  - BASIS (Biology of Ageing e-Science Integration and Simulation system)
  - SBML web-services
  - Discrete stochastic simulator for SBML
  - SBML short-hand (human-readable SBML)
  - Stochastic Petri-Net simulation tool

- Statistical methods development
  - R packages and web-services for calibration of biological models against experimental data (CaliBayes)
  - Design principles for high-throughput experiments
  - Methods for analysis and presentation of stochastic models and data-sets
  - GA-based parameter estimation tool

Thanks to the CISBAN Team