Universal aspects of aging

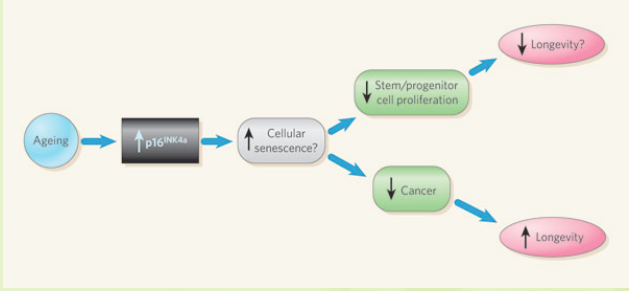
"Age is not a particularly interesting subject. Anyone can get old. All you have to do is live long enough."
–Groucho Marx

A&S300-002 Jim Lund

How can aging be studied?

- Aging has a complex phenotype.
- Studies on humans are difficult:
  - Slow (long lifespan)
  - Expensive
  - Genetic variability
  - Environmental variability

Stem-cell ageing modified by the cyclin-dependent kinase inhibitor $p16^{INK4a}$



Model organisms!

- Small (inexpensive)
- Experimentally tractable
  - Factors that may affect aging can be experimentally manipulated
- Short lifespans
- Controlled environment
- Minimize genetic variation by using inbred animals.

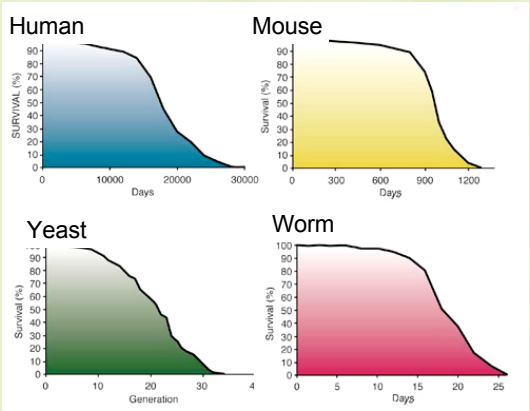
Model organisms

- Examine the aging process in these organisms.
- Aging process is similar in many aspects.
- Different model organisms are good models for different features of aging.

Shared phenotypes

- Aging: increase in mortality rate over time.
- Stress resistance declines (organismal and cellular)
- Physiological function declines with increasing age.
- Diseases of aging.
- Cellular changes in aging cells similar.

Increase in mortality rate over time.



Stress resistance declines

- Studied experimentally in model organisms, generally observed.
  - *S. cerevisiae* (yeast)
  - *C. elegans* (Worm)
  - *D. melanogaster* (fly)
  - *M. musclulus* (mouse)
  - *R. norvegicus* (rat)

Stress resistance declines

- Observed with several different stressors:
  - Heat stress
  - Oxidative stress
    - Hydrogen peroxide, high O_2, paraquat.
  - Heavy metals
  - Osmotic stress

Observed in the aging model organisms.

Stress resistance declines

How are the experiments done?

- Yeast, fly, and worm: whole animal experiments
- Mammals: cell culture.

Observed in the aging model organisms.

Resistance to high O_2 levels declines with age (fly)

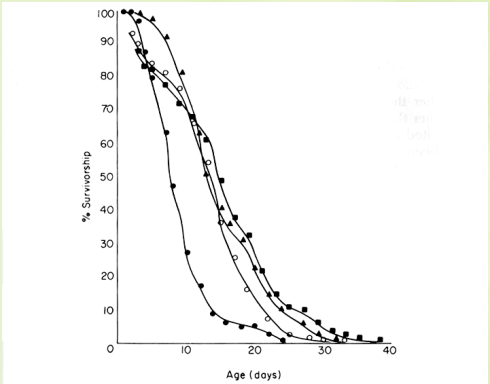
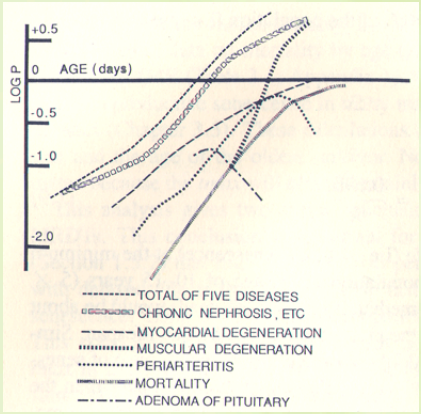


Fig. IV-9. Effect of O_2 tension on survival of *Drosophila melanogaster* [Strehler (582)]. ●, 100% O_2, N = 402; ○, 20% O_2, N = 888; ▲, 2% O_2, N = 247; ■, 1% O_2, N = 240. Remainder of gas mixture consisted of N_2.

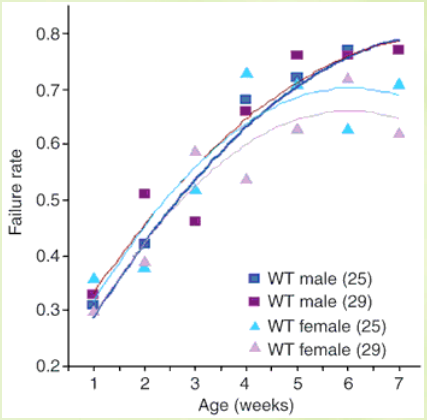
Diseases of aging

- Many can be modeled in aging model organisms.
- Mouse and rat are the closest models.
  - Heart disease, cancer, arthritis, kidney disease, neurodegenerative diseases, etc.
- Some aspects can be modeled in fly and worm.
  - Models for Alzheimer's disease and other types of neurodegeneration
  - Aspects of heart disease seen in the fly.

Disease incidence increases with age in the mouse



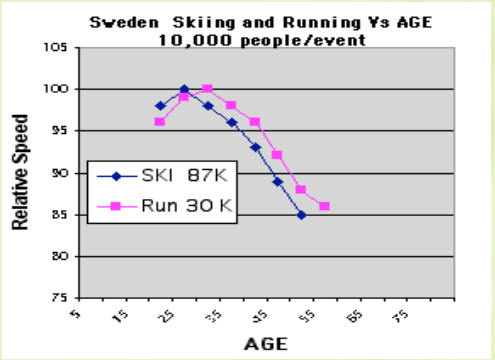
Heart disease in *D. melanogaster* (fruit fly)



Parallels in the decline in physiological function in model organisms.

- Generally conserved to the extent that the physiology is conserved.
- For example, worm/fly/mouse/rat have muscle cells, and a decline in muscle function is observed as these animals age, modeling the decline in muscle and sarcopenia in humans.

Human: Ave. Performance vs Age



- **Averaging the performance of large numbers of people removes many variables including conditioning and talent.**
- LE Bottiger. Brit. Med. J. **3;** 270-271, 1973

Movement and defecation declines in old *C. elegans*

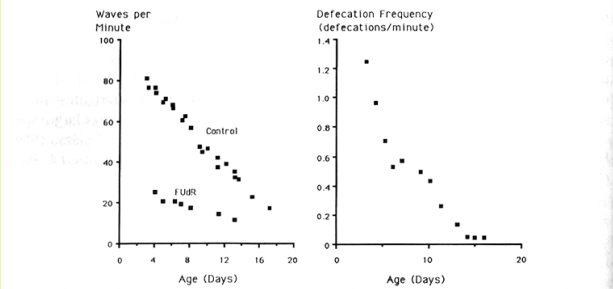


Fig. 2.20. Age-related changes in *Caenorhabditis elegans*. *Left*, whole-body (sinusoidal) movements in control and populations treated with FUdR, a halogenated nucleoside that blocks all DNA synthesis and cell division; despite major effects of FUdR on body movement, the lifespans were not altered. *Right*, defecation frequency shows nonmonotonic changes with age. The regression lines in the original report are not shown. Redrawn from Bolanowski et al., 1981.

Cellular changes in aging cells

- Nuclear changes
  - Nucleus enlarges.
  - Nucleolus: changes morphology, undergoes fragmentation.
- Reduced efficiency of DNA repair.
- Total gene transcription lower.
- Altered gene transcription.
- Protein turnover declines.
- AGEs (Advanced Glycation End-products)

- **Aging changes present in most organisms!**

Cell loss during aging

- Loss of non-dividing cells: fly, mouse, rat, human.

- Loss of renewing cell populations:
  - Somatic cells will divide a certain number of times and then stop (senesce).
  - Senescent cells have an altered phenotype.
  - Mouse, rat, human.

Cellular damage in aging cells

- Nuclear and mitochondrial DNA mutations.
- Lipid peroxidation.
- Lipofuscin deposits.
- Protein crosslinks, protein aggregates.

- **Aging changes seen in most organisms!**

Why use model organisms?

- Concentration of work on an organism allows particularities of aging to be well-characterized.
- Researchers can build on previous studies and thus the experiments proceed faster and can investigate in more depth.
- Genomes sequenced and best characterized, genome manipulation technologies best developed.

Discoveries validate these aging models

- Treatments that extend lifespan typically work in multiple organisms!
- Conserved genes that affect the rate of aging do so in multiple organisms!