The Biology of Aging: An Overview

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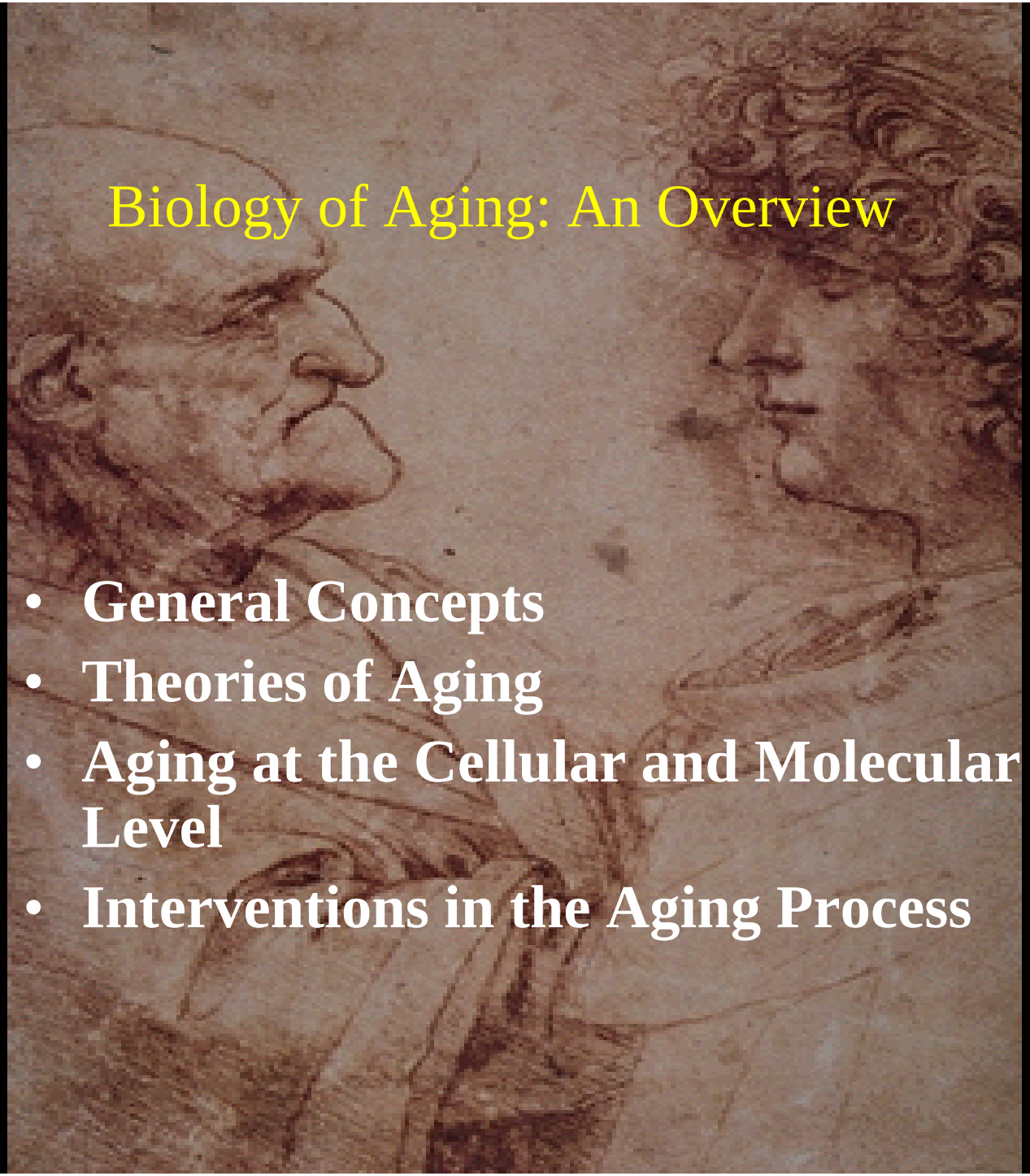
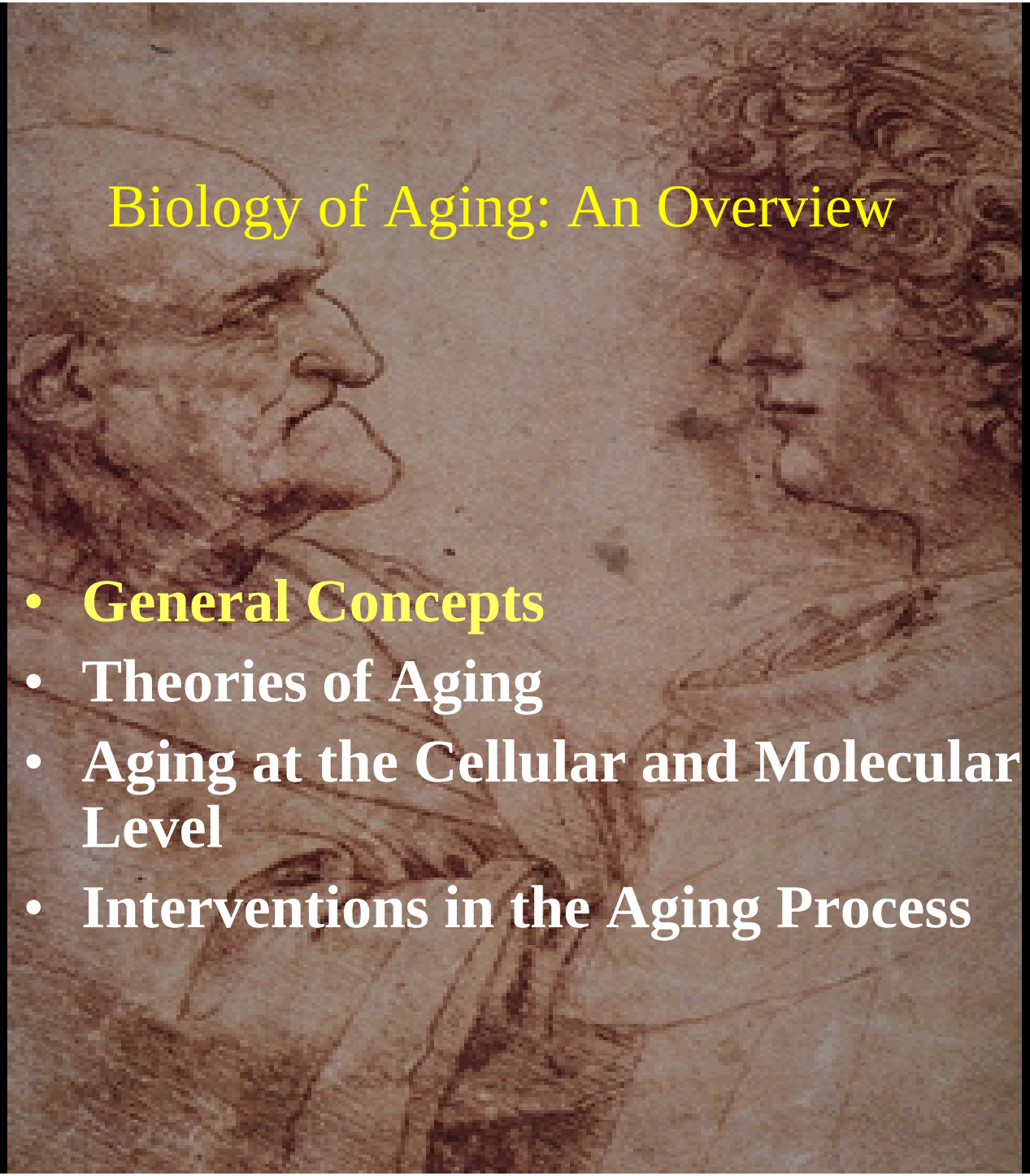


Biology of Aging: An Overview

- **General Concepts**
- **Theories of Aging**
- **Aging at the Cellular and Molecular Level**
- **Interventions in the Aging Process**



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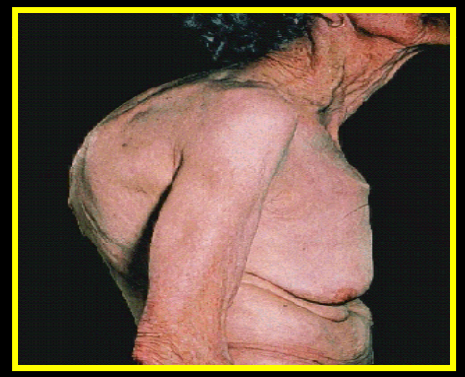
Aging v. Senescence

Beneficial

Neutral



Deleterious

Universality of Aging

- No evidence that prokaryotes undergo senescence
- Populations of single-celled eukaryotic organisms are immortal
- In multicellular organisms, senescence occurs in those that undergo somatic cell differentiation

Masoro, E in Handbook of Physiology, Aging, Section 11:3-21 (1995).

Rates of Senescence

- RAPID: occurs abruptly after maturation (e.g. nematodes, flies) or soon after reproduction (e.g., annual plants, Pacific salmon)
- GRADUAL: slow but persistent deterioration after maturation in all placental mammals
- NEGLIGIBLE: no clear evidence for postmaturational increases in mortality rate (e.g., clams, trees, fish, reptiles)

Finch, CE in Longevity, Senescence, and the Genome (1994).

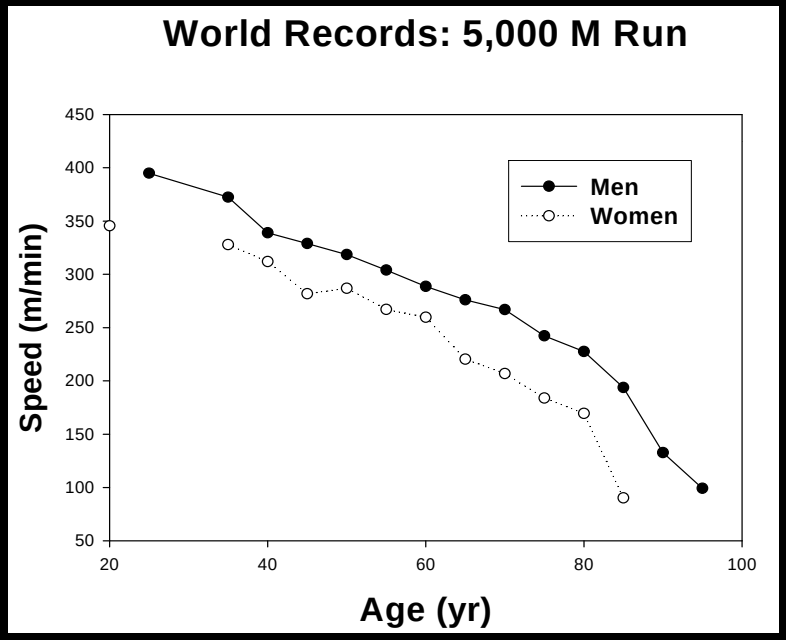
Q: Which of the following is ***true*** with regard to primary aging processes?

- They are deteriorative changes over time in the relative absence of disease or injury.
- Protection against premature death underlies survival increases that would otherwise be reduced secondary to primary aging processes.
- They do not influence maximum life span.
- They are not thought to be the underlying cause of senescence across species.

Primary Aging Processes

- Deteriorative changes over time in the relative absence of disease or injury
- Influence maximum life span
- Thought to be the underlying cause of senescence across species

Primary aging processes occur in the absence of disease



Bill Collins
World's Fastest 50 Year Old

Age 17

Age 52

Median Length of Life

- Age at which there are as many individuals with shorter life spans as there are with longer ones
- Protection from premature death underlie survival increases
- Thought NOT to reflect primary aging processes

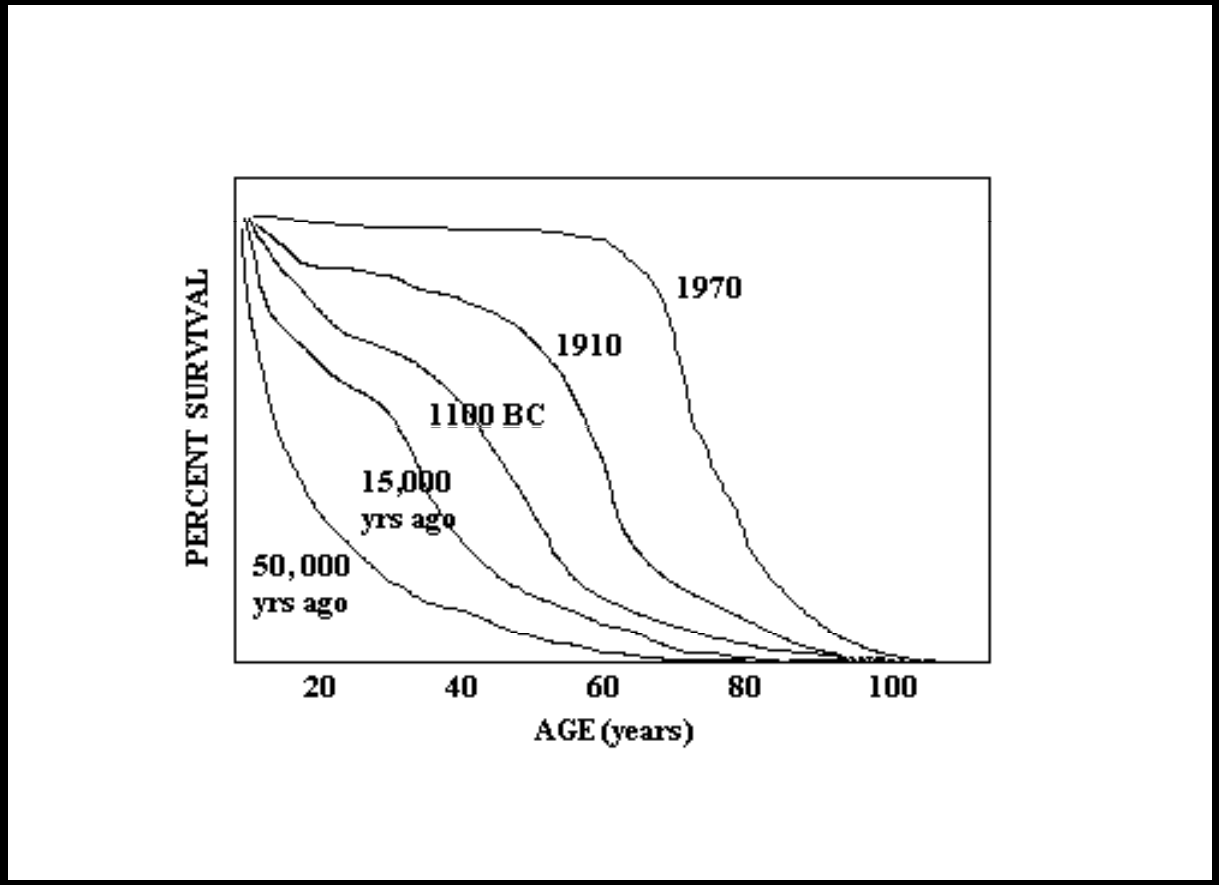
Maximum Life Span

- Age of the longest-lived survivors of a cohort or population
- For humans, operationally considered to be the oldest age reached by 1 in 100 million people
- Considered to be inversely proportional to the rate of aging of a population

Q: All of the following resulted in a dramatic increase in average life span in the early 1900s ***except***:

- [ ] Sanitation
- [ ] Immunization
- [ ] Better nutrition
- [ ] Antibiotics

Human Survivorship through History

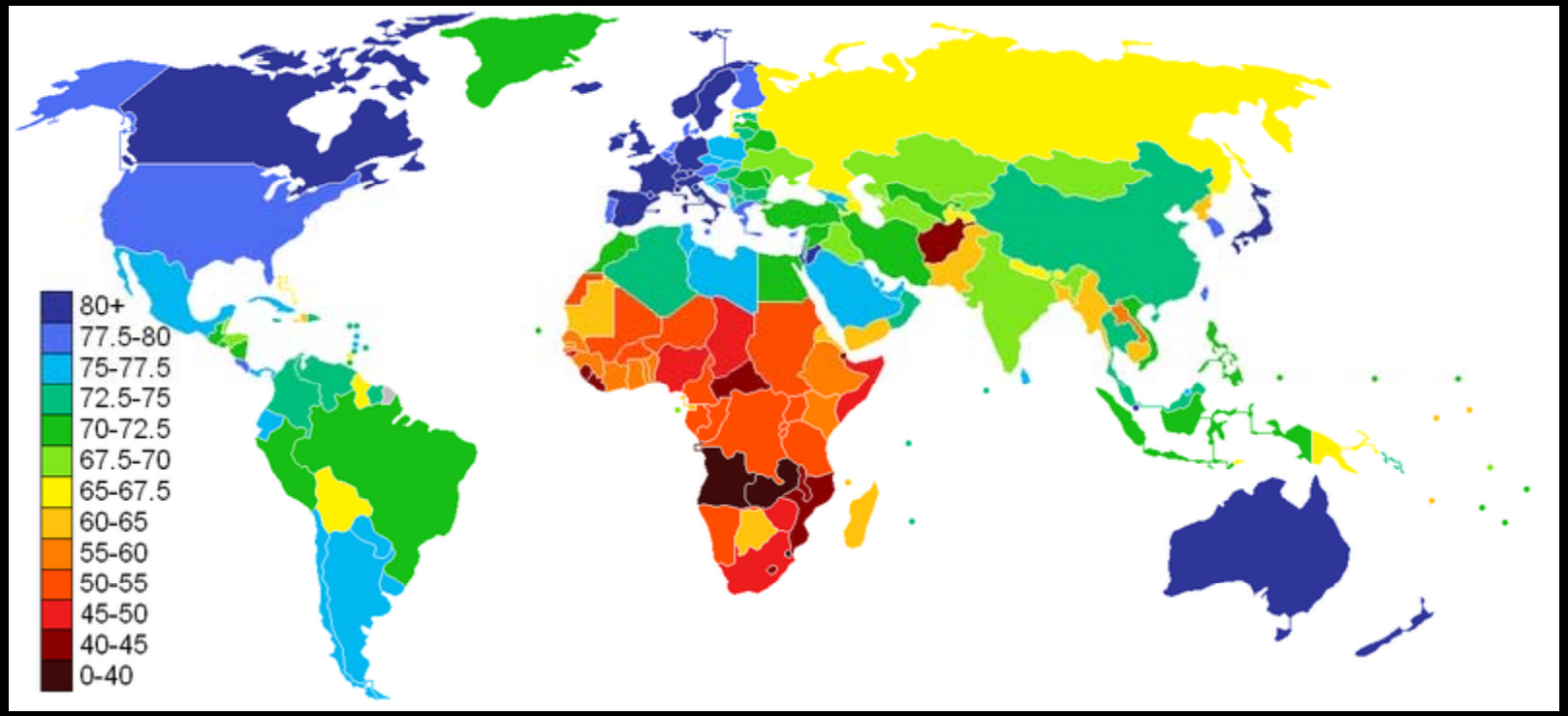


Pignolo, RJ & Forciea, MA, in *Geriatric Secrets*, pp 7-13 (2004)

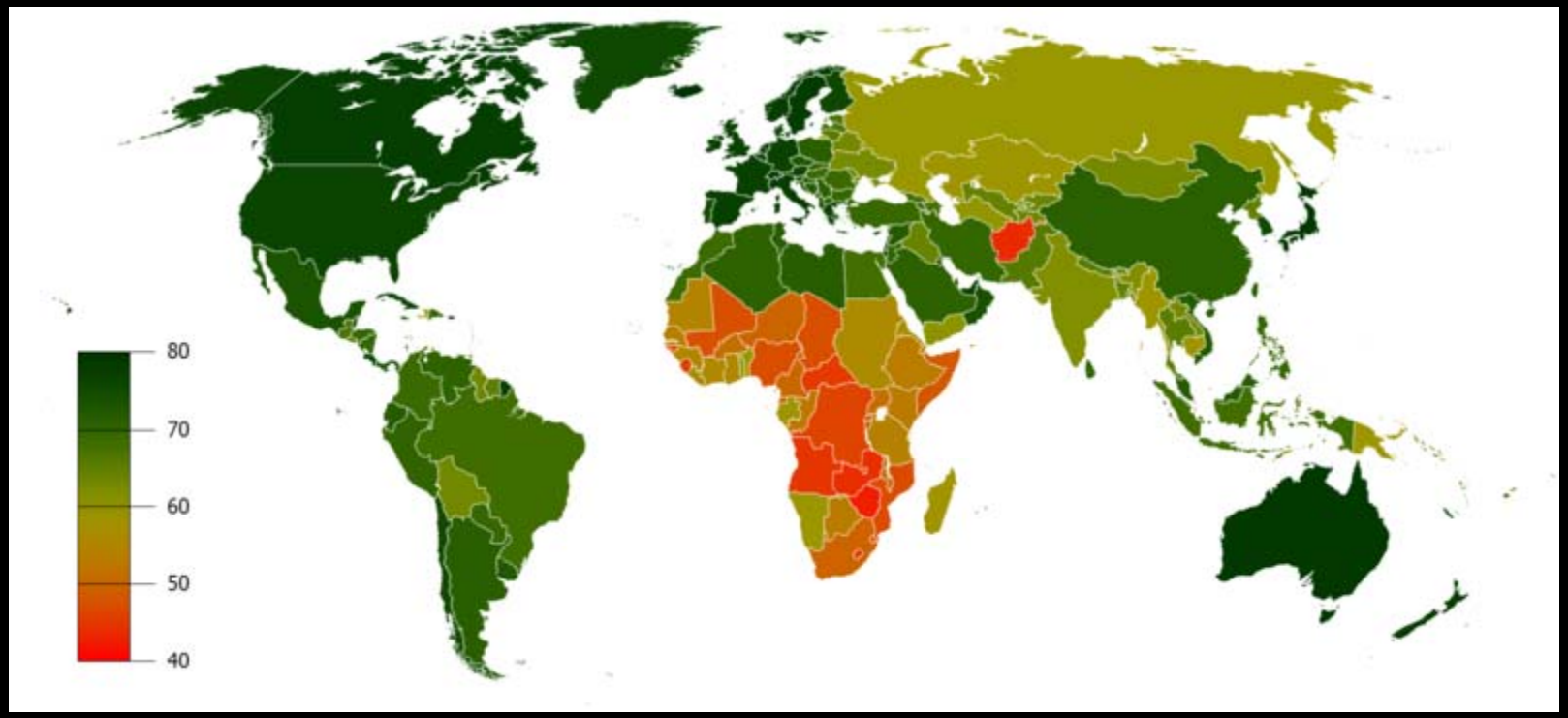
Life Expectancy List by the United Nations (2005-2010)

Rank	Country	Life expectancy at birth (years) Overall	Life expectancy at birth (years) Male	Life expectancy at birth (years) Female
1	Japan	82.6	78.0	86.1
2	Hong Hong	82.2	79.4	85.1
3	Iceland	81.8	80.2	83.3
4	Switzerland	81.7	79.0	84.2
5	Australia	81.2	78.9	83.6
6	Spain	80.9	77.7	84.2
7	Sweden	80.9	78.7	83.0
8	Israel	80.7	78.5	82.8
9	Macau	80.7	78.5	82.8
10	France (metro)	80.7	77.1	84.1
11	Canada	80.7	78.3	82.9
12	Italy	80.5	77.5	83.5
36	United States	78.3	75.6	80.8

Life Expectancy at birth



Male Life Expectancy



Longest-lived Humans

Jeanne Calment (France)
Lived to age 122

Christian Mortensen
(Danish-American)
Lived to age 115

Robine, J-M & Allard, M, Science 279: 1834-5 (1998).
Deianna, L et al. JAGS 50: 2098-9 (2002).

Q: Examples of long-lived human populations point to which of the following pro-longevity factor(s):

- [ ] Genetic pre-disposition
- [ ] Dietary practices
- [ ] Spirituality
- [ ] Conformity to beneficial health practices
- [ ] All of the above

The places where people live the longest

- Okinawa, Japan
- Ovodda, Sardinia (Italy)
- Loma Lida, CA (USA)

Keys to longevity-Okinowa

- “hara haci bu”
- Rainbow diet
- Diet: soy > fish, meat, eggs, dairy
- BMI 20.4
- ~1200 cal diet
- DHEA levels decline more slowly

Keys to longevity- Ovodda, Sardinia

- As many men live to 100 as women
- Sardinians who emigrated at 20, 30 or 40 years of age still manage to reach 100
- Descended from only a few original settlers – isolated, interbreeding
- G6PD deficiency, other genetic traits?

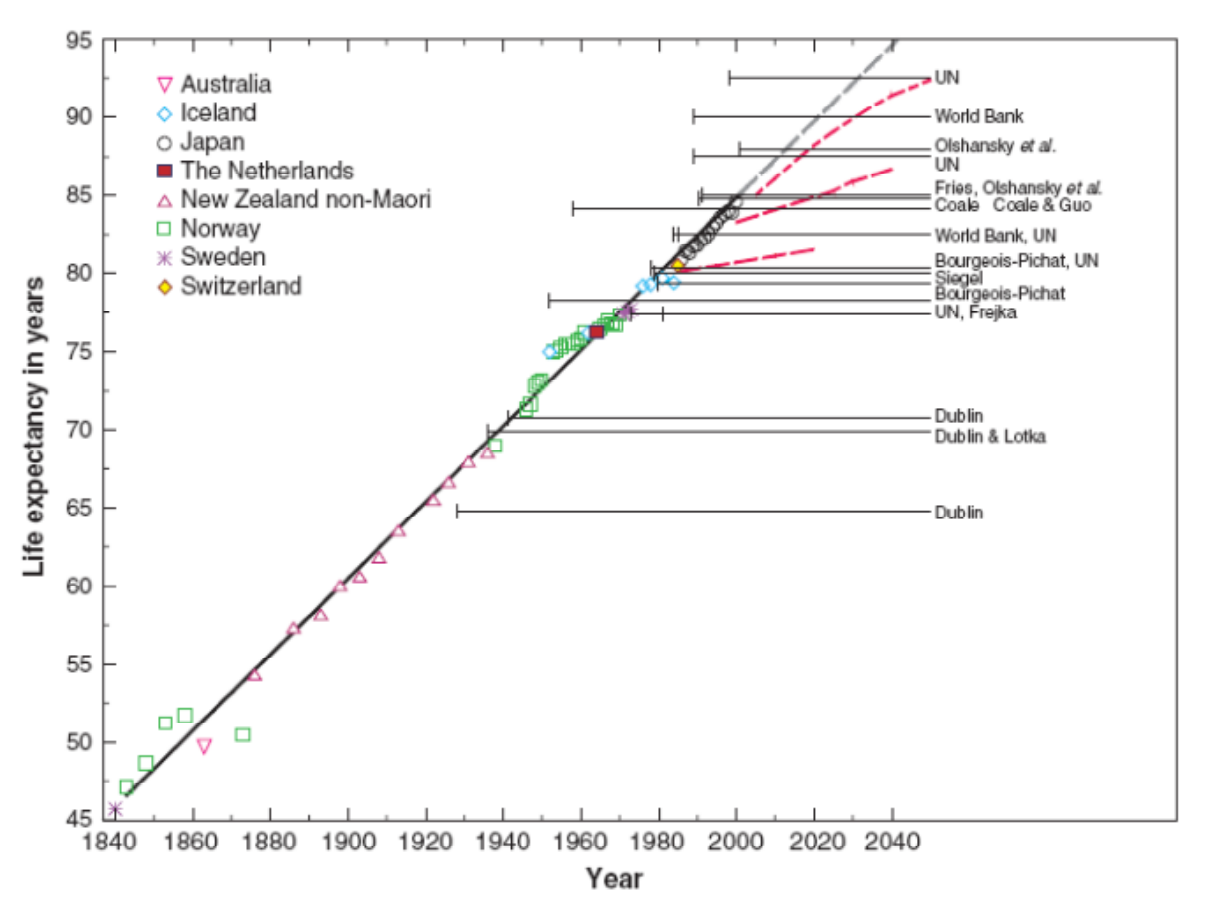
Keys to longevity- Loma Linda, CA

- Seventh Day Adventists
- Members live 5-10 years longer than fellow citizens
- No drinking or smoking
- Many adhere to a vegetarian diet the church advises
- Spiritual life
- Regular churchgoers – of whatever faith - live longer
- Significantly lower levels of stress hormones

Keys to longevity

"How long would you live if you were a Sardinian 7th Day Adventist who moved to Okinawa at 20 years of age?"

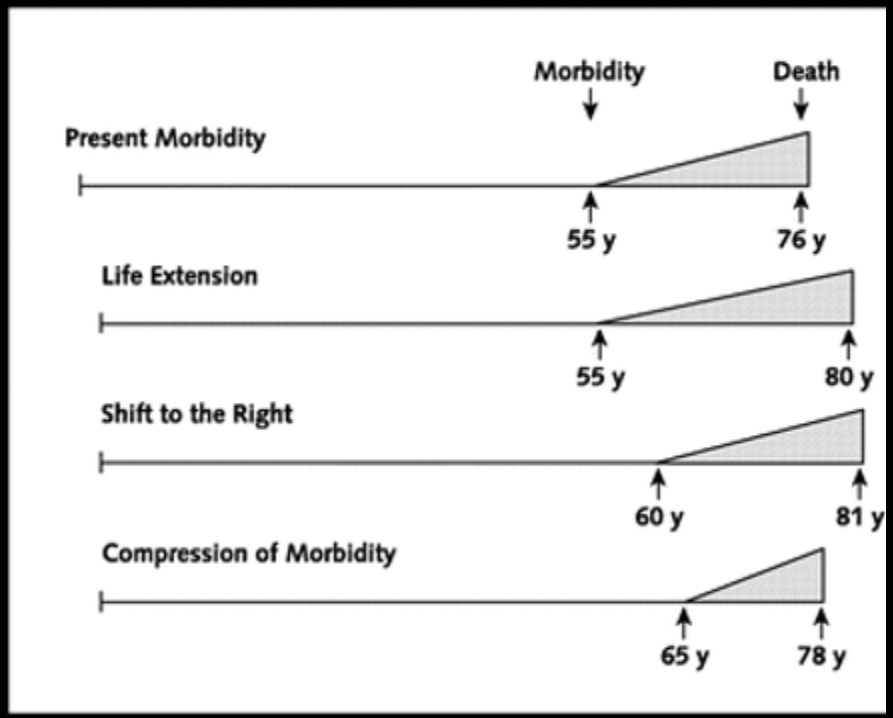
Broken Limits to Life Expectancy



Female life-expectancy in Japan has risen for 160 years at a steady pace of almost 3 m/yr!

Oeppen & Vaupel Science 296: 1029-31 (2002)

Compression of Morbidity



Fries, JF Ann Int Med 139:455-9 (2003)

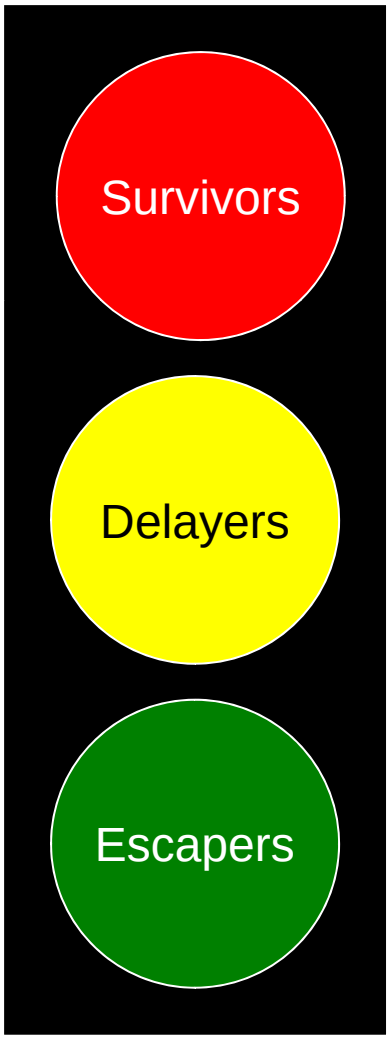
Q: Which is ***true*** regarding morbidity with increased life span as reflected by disability trends?

- Morbidity increases with life extension.
- Morbidity remains the same with increased life span.
- Morbidity is compressed.

Q: Which of the following is ***true*** regarding the onset of age-related disease in centenarians?

- Age-related disease is delayed by almost one decade.
- Age-related disease occurs at about the same time in centenarians as in individuals with average life expectancy.
- Age-related disease does not occur in centenarians.
- Age-related disease may occur at about the same time as in individuals with average life spans, may be delayed or even absent in centenarians.

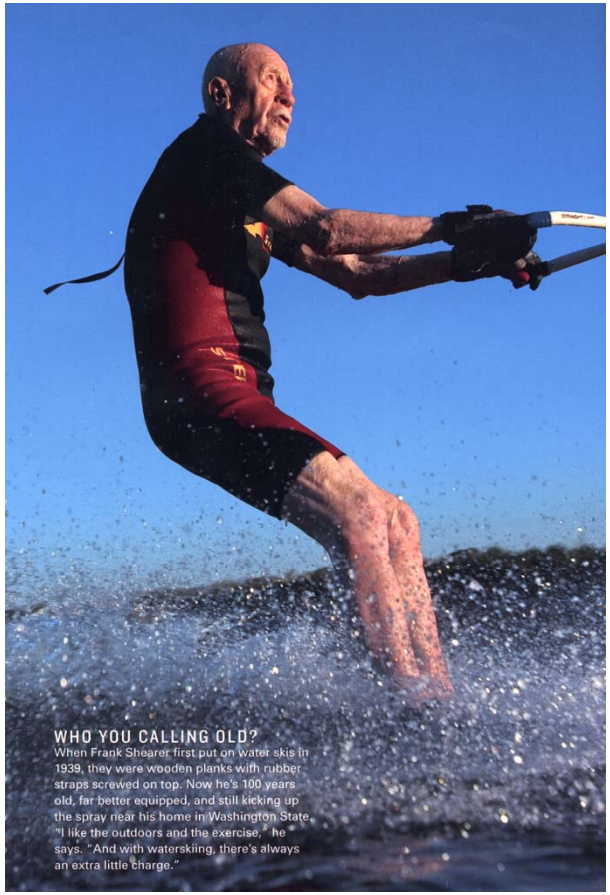
Who are centenarians?



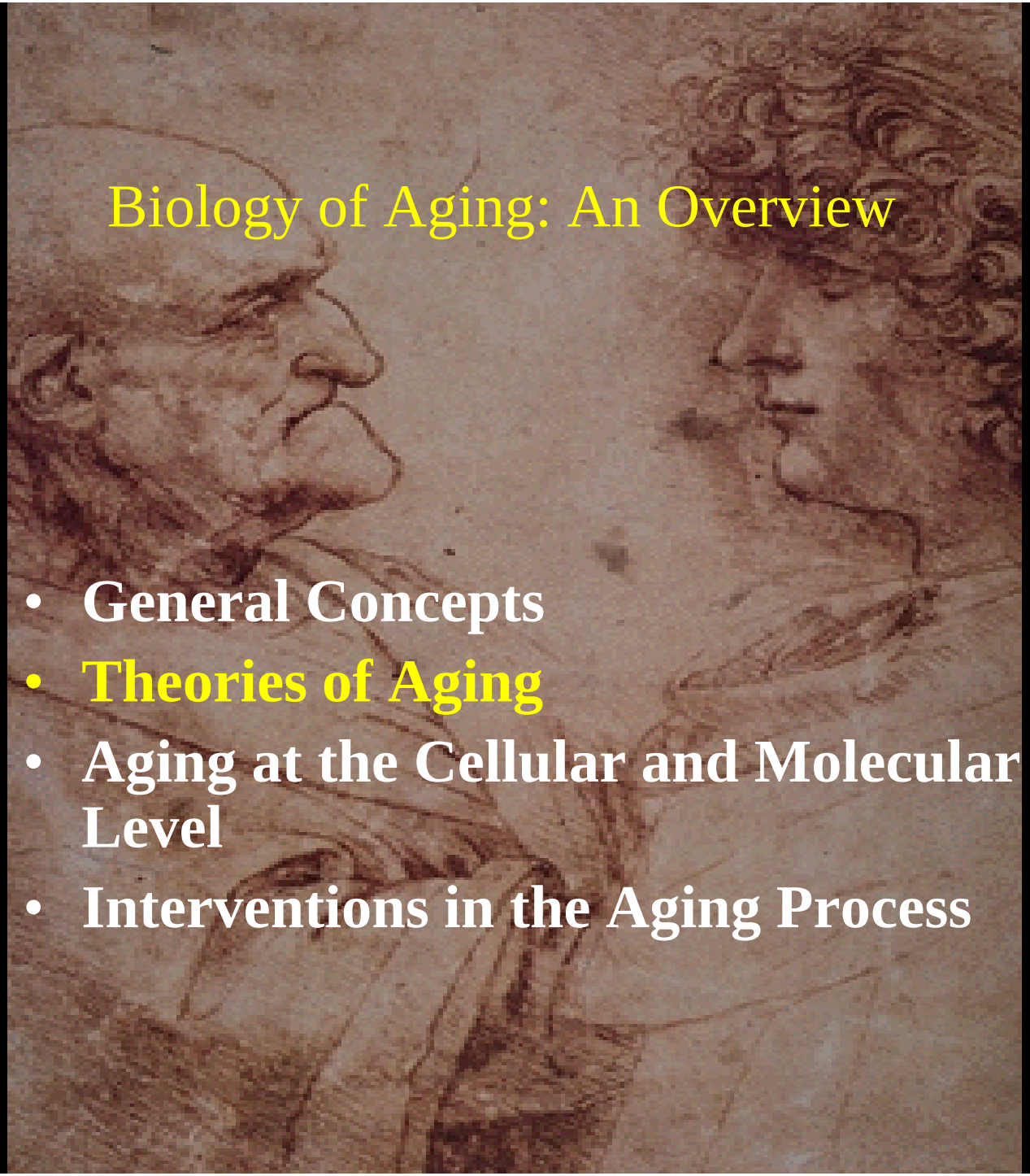
Characteristics of Aging	Examples
Increased mortality after maturation	Survival curves showing exponential increase in mortality with age
Changes in biochemical composition of tissues	Increases in lipofuscin or age pigment Increased cross-linking in extracellular matrix molecules such as collagen
Progressive, deteriorative physiologic changes	Declines in glomerular filtration rate, maximal heart rate, vital capacity
Decreased ability to adaptively respond to environmental changes	Decreased "first past" hepatic metabolism Blunted maximal cardiac responses to exercise
Increasing incidence of many diseases	Ischemic heart disease, type II diabetes, osteoporosis, Alzheimer's disease

Cristofalo, VJ, Gerhard, GS & Pignolo, RJ Surg. Clin. N. Am. 74: 1-21 (1994).

Characteristics of Aging	Exceptions
Increased mortality after maturation	Human age-specific mortality rates do not continue to increase exponentially at very advanced ages
Changes in biochemical composition of tissues	Changes are quite heterogeneous from organ to organ within a specific individual and also from individual to individual ("usual" and "successful" aging)
Progressive, deteriorative physiologic changes	" "
Decreased ability to adaptively respond to environmental changes	" "
Increasing incidence of many diseases	Elimination of atherosclerosis and cancer as causes of death would only add about ten years to average life span and would not affect maximum life span potential



WHO YOU CALLING OLD?
When Frank Shearer first put on water skis in 1939, they were wooden planks with rubber straps screwed on top. Now he's 100 years old, far better equipped, and still kicking up the spray near his home in Washington State. "I like the outdoors and the exercise," he says. "And with waterskiing, there's always an extra little charge."



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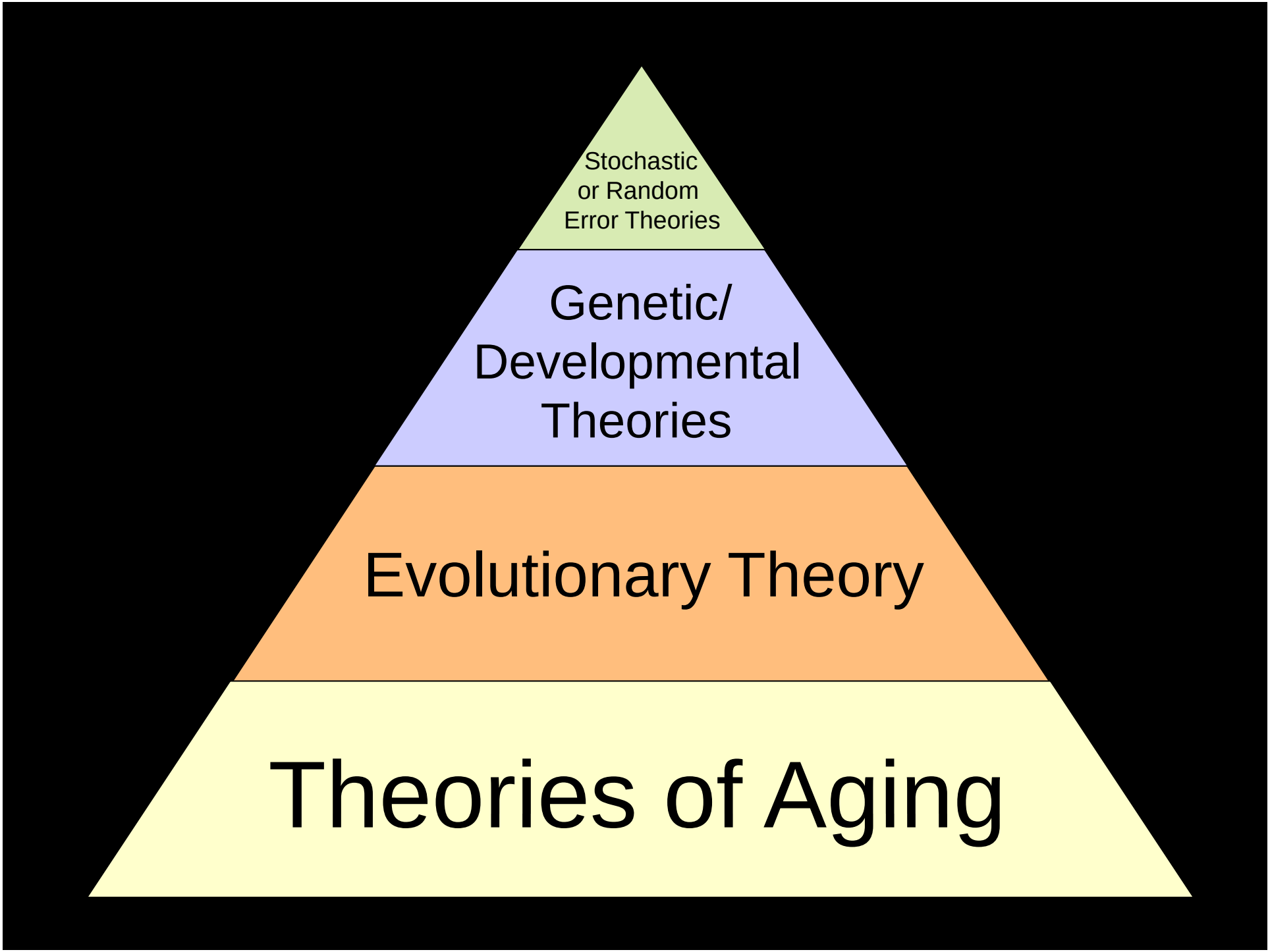
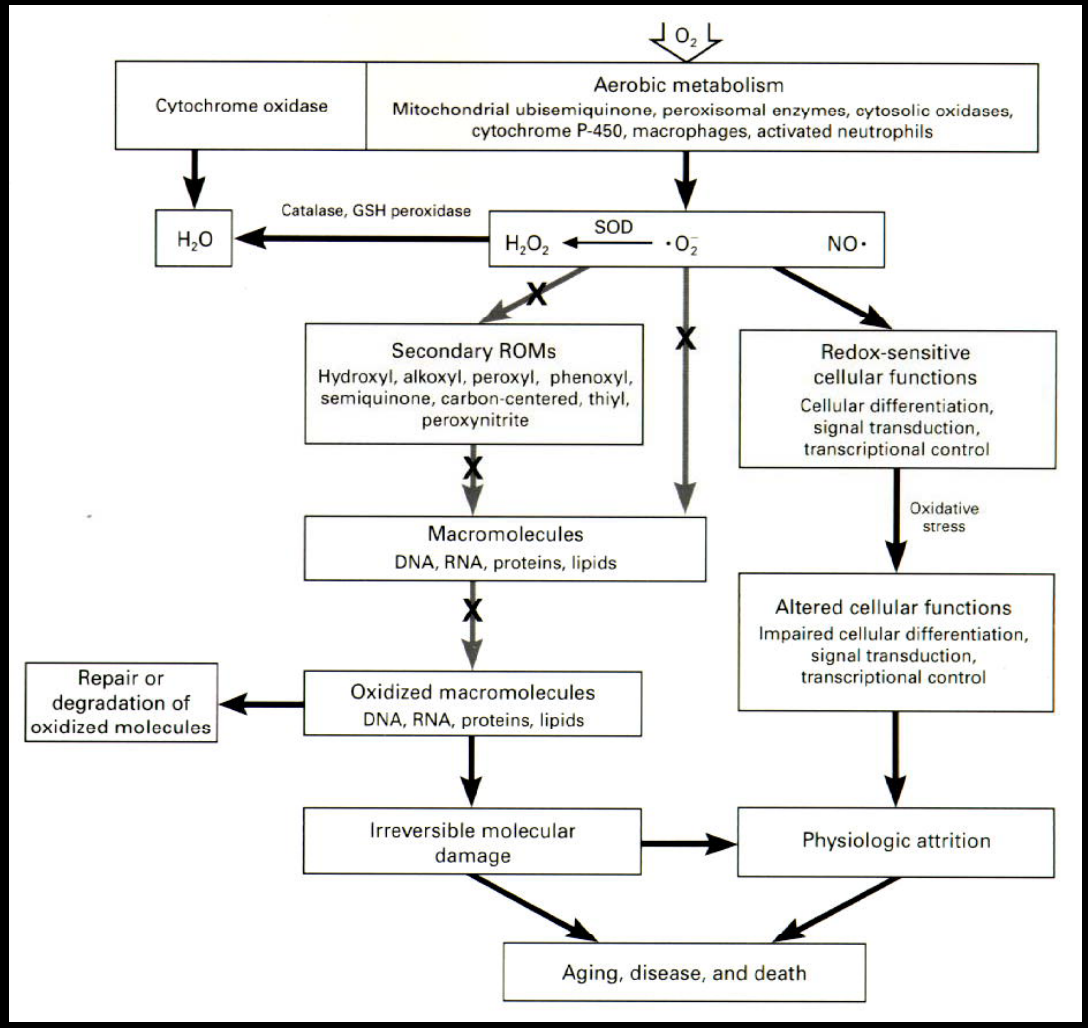

Stochastic
or Random
Error Theories
Genetic/
Developmental
Theories
Evolutionary Theory
Theories of Aging

Cumulative Oxidative Damage during Aging



Weindruch, R & Sohal, RS NEJM 337: 986-94 (1997).

Q: All of the following evidence supports a genetic basis for longevity, ***except***:

- Common polymorphisms in the APOE gene have a modest effect on life span.
- There is high conservation of maximum life span seen between species .
- There are examples of exceptional longevity within families.
- Twin studies demonstrate that genetic differences likely account for about 50% of the variance in adult human life span.

Genetic Basis of Aging Theories

- High conservation of maximum life span between species
- Similarity of attained age between monozygotic twins compared to dizygotic twins or nontwin siblings
- Examples of exceptional longevity within families
- Subsets of aging features in human genetic syndromes of premature aging

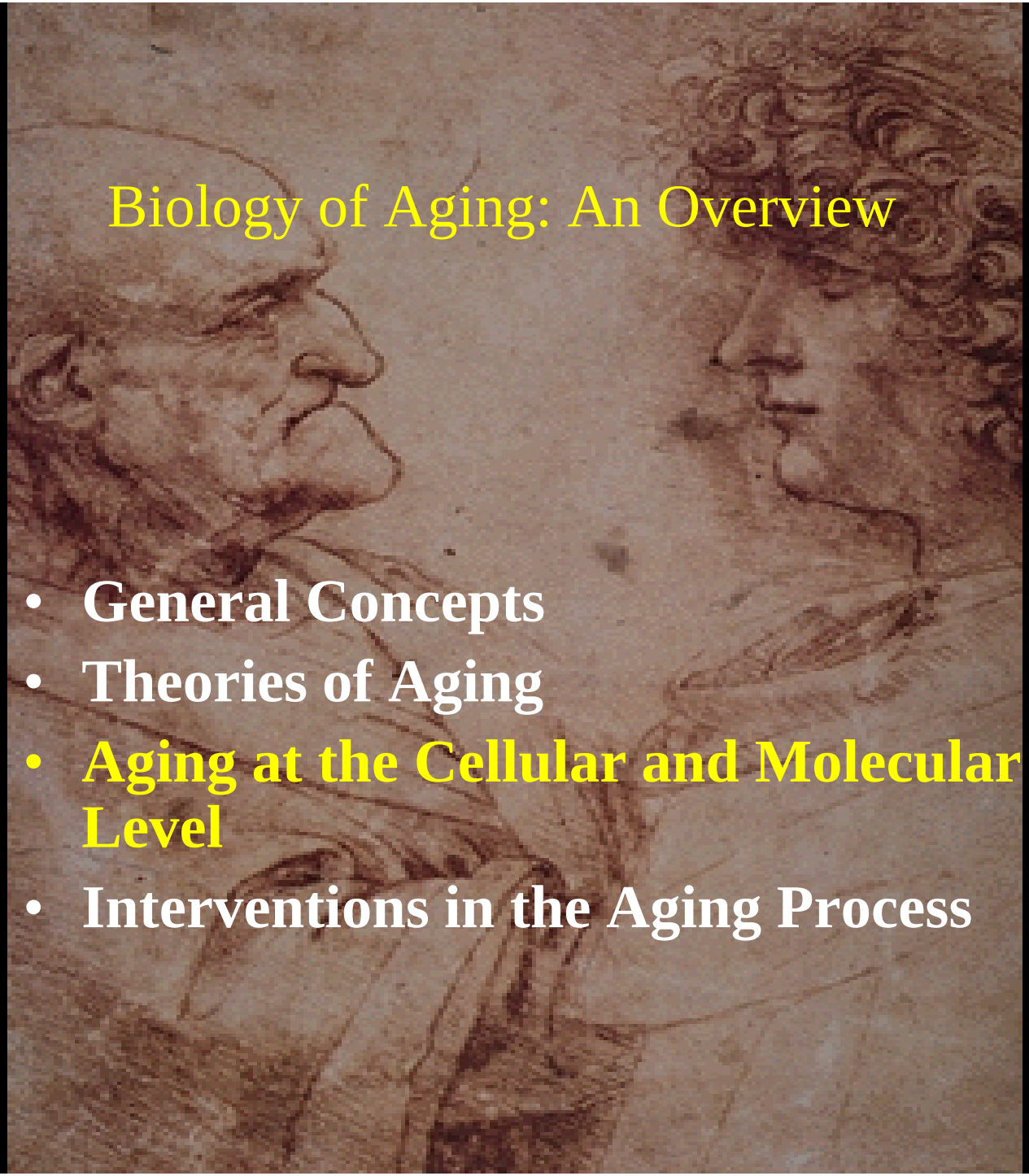
Most commonly described human segmental progeroid syndromes.

Syndrome	Incidence (per live birth)	Inheritance	Mean life-span (years)	Progeroid features	Genome maintenance defect
Hutchinson-Gilford	<1/1,000,000	Unknown	~13	Alopecia, sclerosis, wrinkling, soft tissue, cachexia, arteriosclerosis, diminished fat	Laminin
Werner	<1/100,000	Autosomal recessive	~50	Alopecia, osteoporosis, malignancies, arteriosclerosis, diabetes, cataracts, telangiectasia, skin atrophy, graying of hair	DNA helicase (RecQ-like), exonuclease
Rothmund-Thomson	<1/100,000	Autosomal recessive	Normal ?	Alopecia, malignancies, poikiloderma, cataracts, osteoporosis, graying of hair	DNA helicase (RecQ-like)
Cockayne	~1/100,000	Autosomal recessive	~20	Thin hair, cachexia, retinal degeneration, hearing loss, neurodegeneration (cerebellar ataxia), cataracts	Transcription-coupled DNA repair
Trichothiodystrophy	<1/100,000	Autosomal recessive	~10	Cachexia, osteoporosis, cataracts, fragile hair, neurodegeneration (cerebellar ataxia)	DNA repair, basal transcription
Ataxia telangiectasia	~1/60,000	Autosomal recessive	~20	Skin atrophy/sclerosis, telangiectasia, immunodeficiencies, malignancies, graying of hair, poikiloderma, neurodegeneration (cerebellar ataxia)	DNA damage signaling protein kinase
Down	~1/1,000	De novo	~60	Cataracts, graying of hair, alopecia, diminished subcutaneous fat, vision loss, neurodegeneration (Alzheimer-like), thyroid dysfunction	Trisomy

Adapted from Hasty, P et al. Science 299: 1355-59 (2003).

Evolutionary Theory

- Risk of mortality increases with time after reproduction
- Genes that confer early benefits on reproductive fitness are selected, even if they cause deleterious effects later in life
- No selective pressure against genes that confer negative effects later in life
- Strong pressure to retain genes that diminish vulnerability in young and old alike



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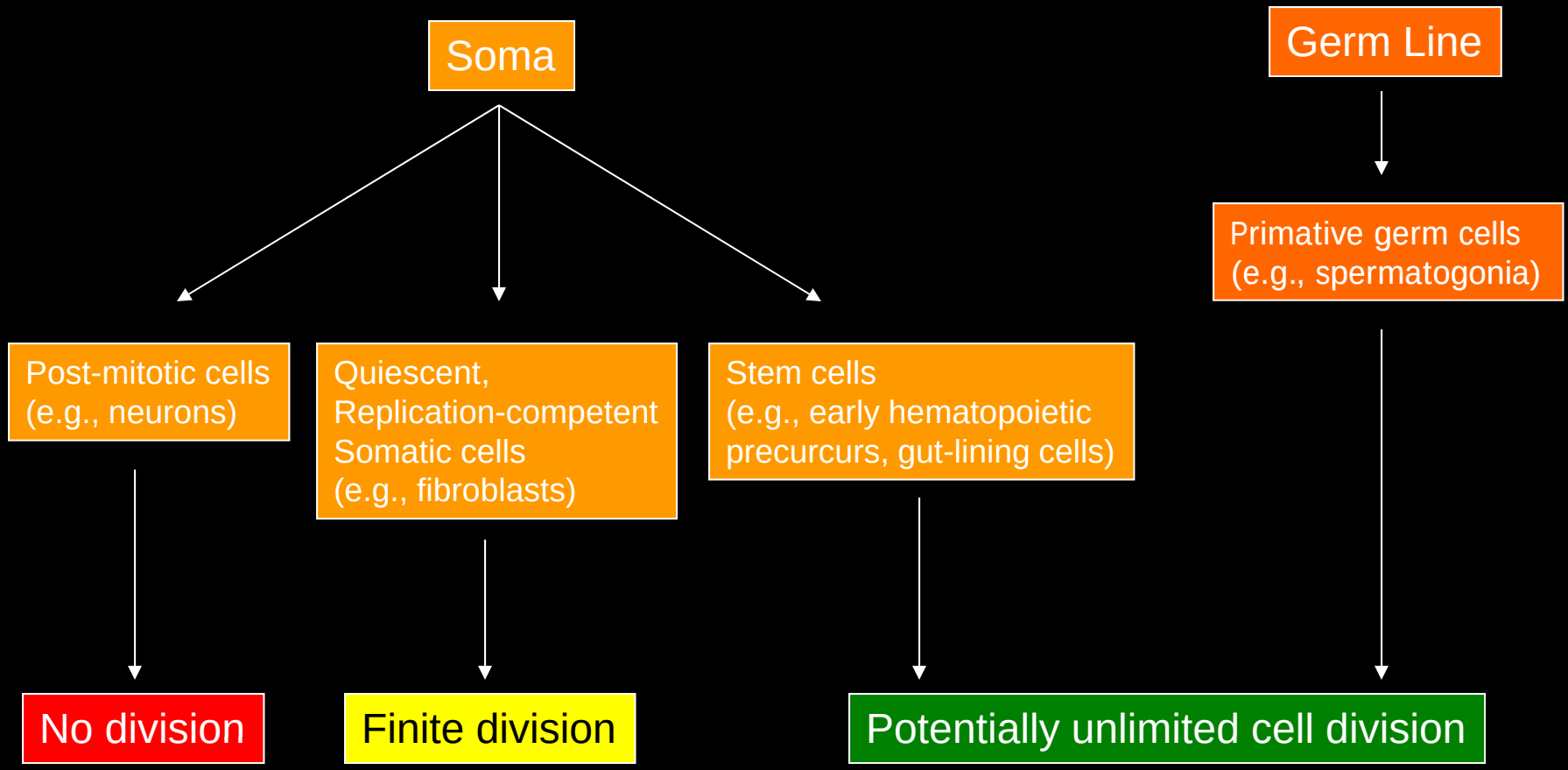
Replication Potential of Normal Human Cells

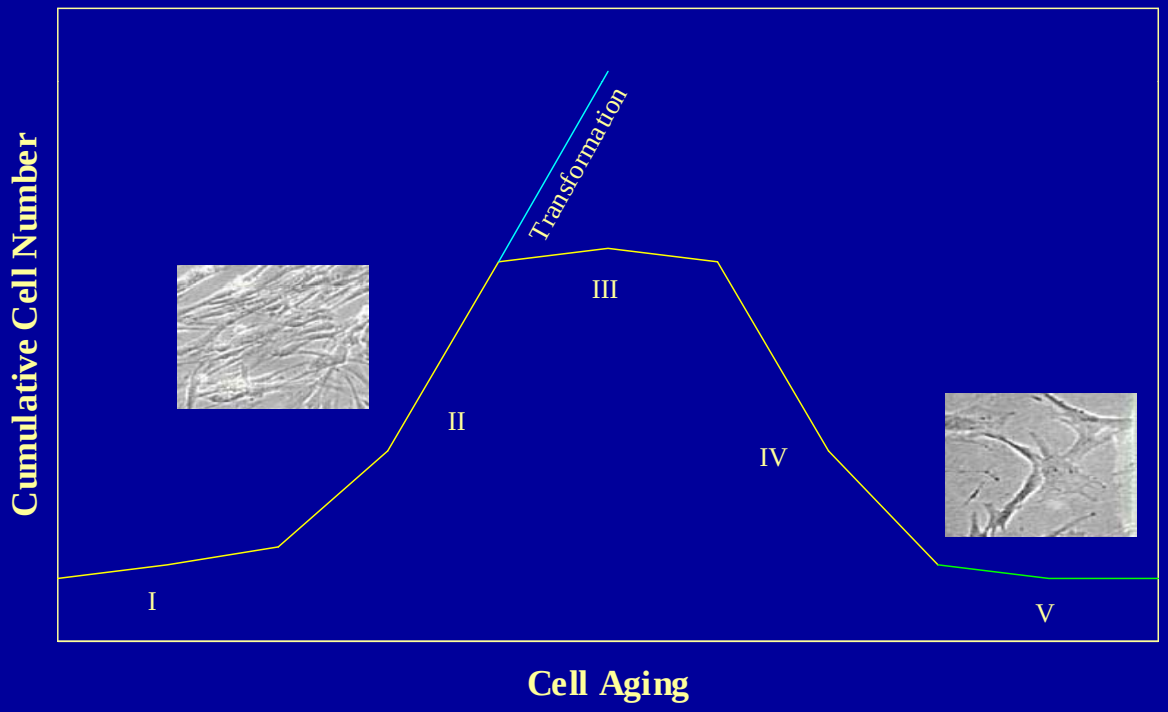


Q: Some characteristics associated with replicative senescence include all of the following ***except***:

- Apoptosis resistance
- Finite replicative life span
- Altered pattern of gene expression
- Promotion of intrinsic aging in all cell types
- Essentially irreversible growth arrest.

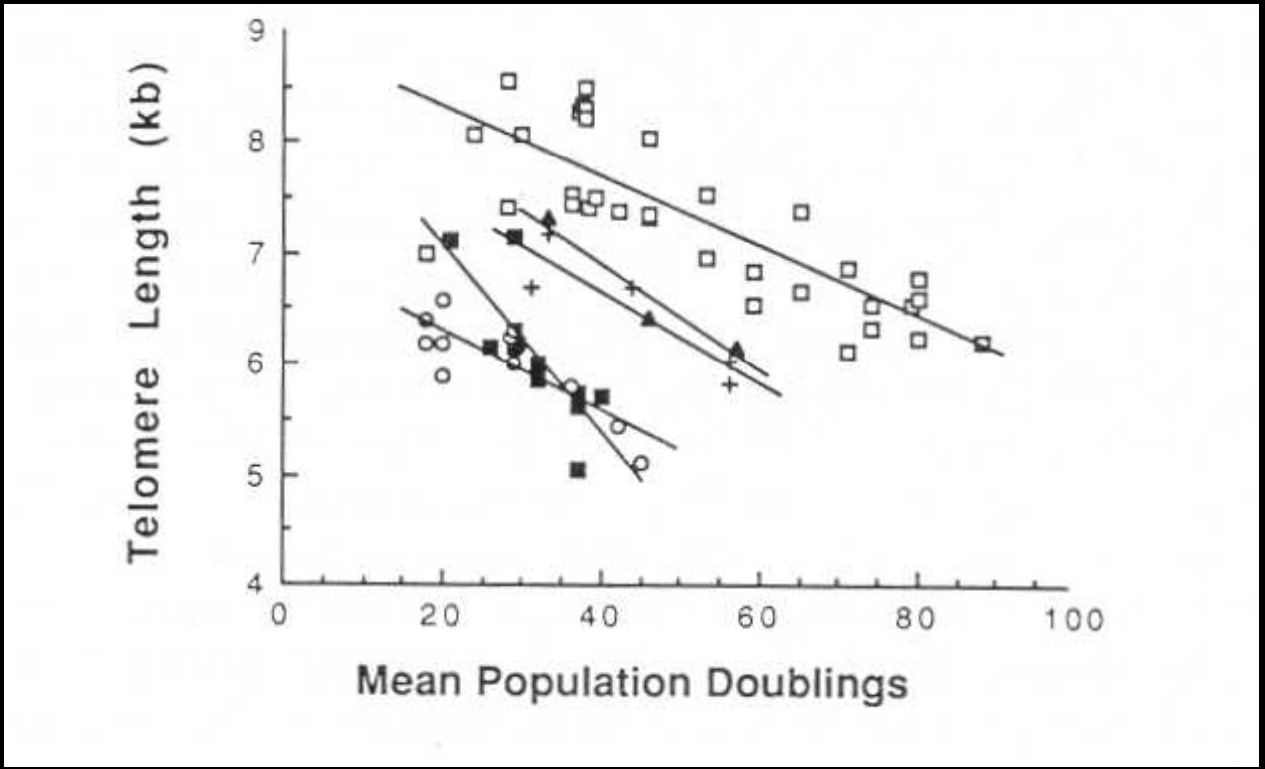
Cellular (Replicative) Senescence

Stages in the in vitro life history of normal human diploid fibroblasts



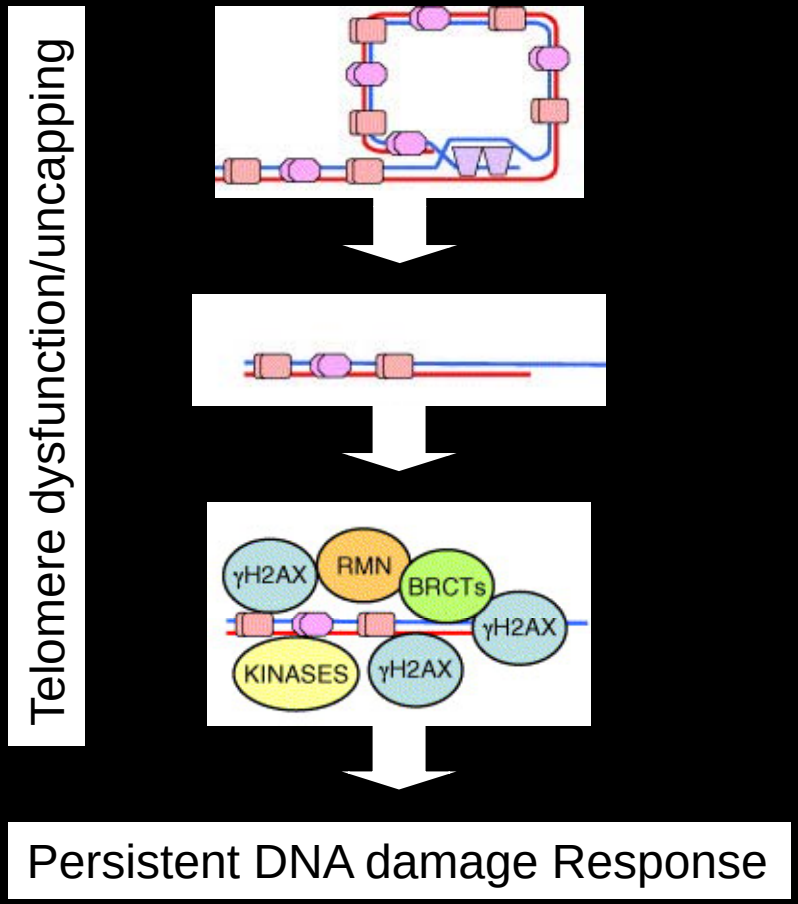
Adapted from Cristofalo, V.J. and Pignolo, R.J. Handbook of the Physiology of Aging, Oxford University Press, 1995.

Telomere Shortening with Cellular Aging



Harley, CB et al. , Nature 345: 458-60 (1990).

Telomere dysfunction



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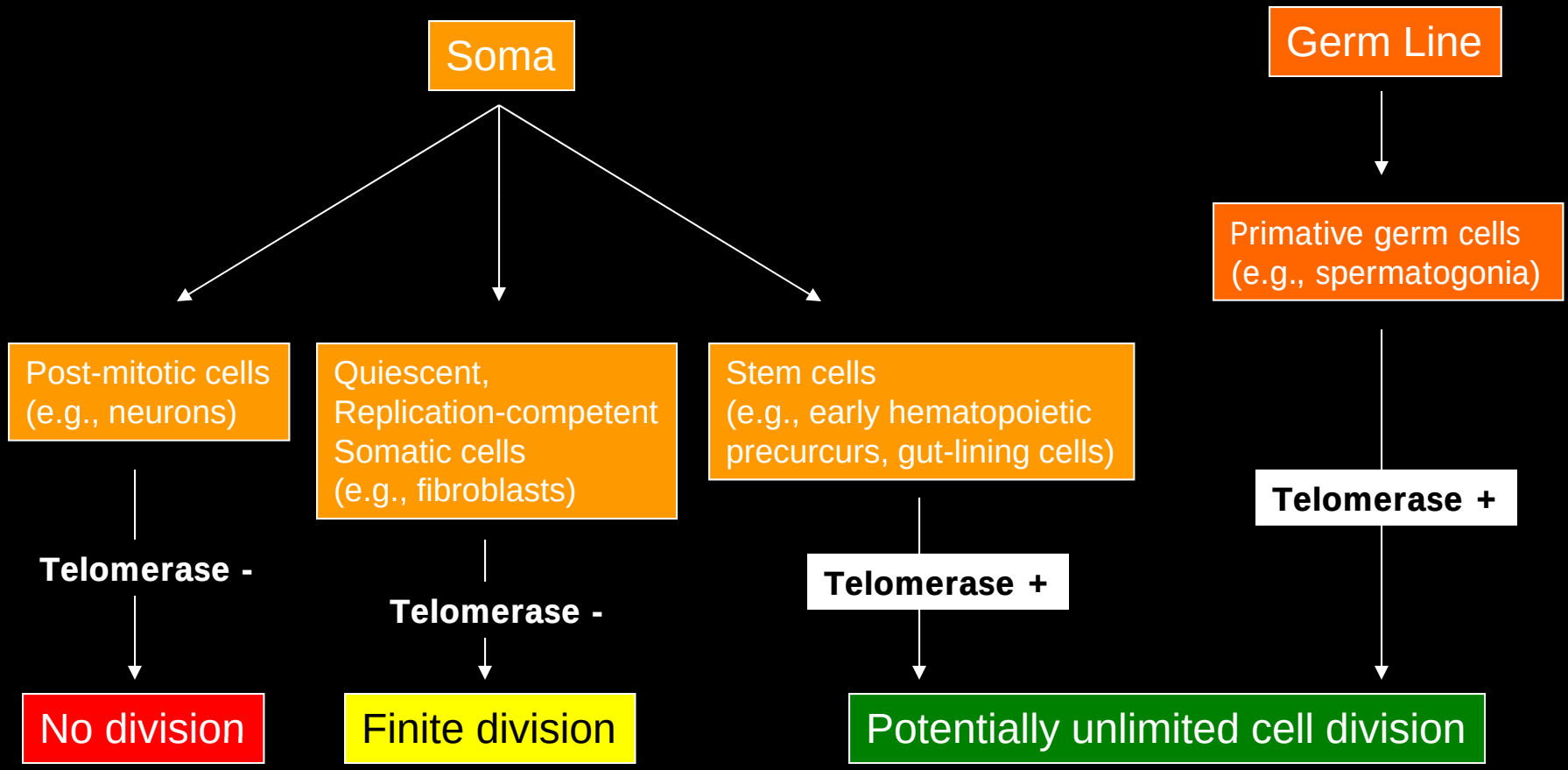
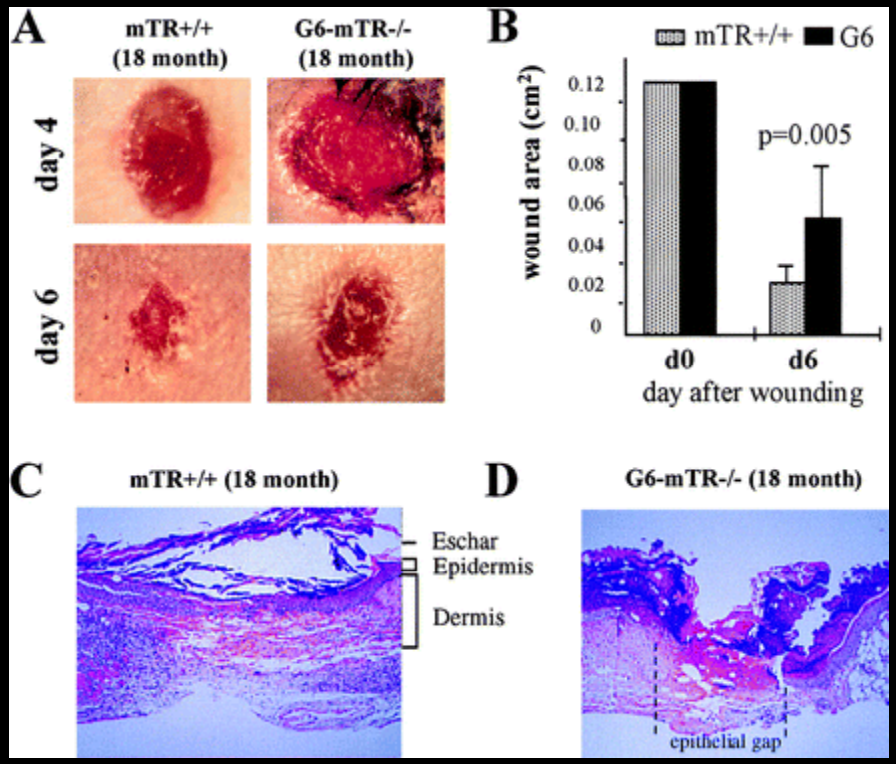


Aging in Telomerase-deficient mice

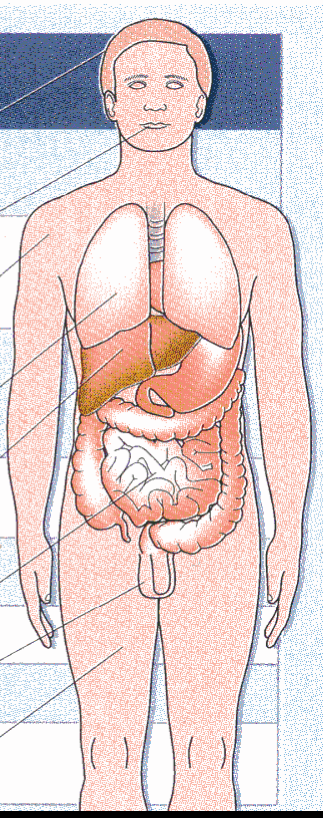
- Age-dependent telomere shortening
- Genomic instability
- Shortened life span
- Reduced capacity to respond to stressors
- Increased spontaneous malignancies
- Villi atropy of small intestine



Rudolph, KL et al. Cell 96: 701-12 (1999).

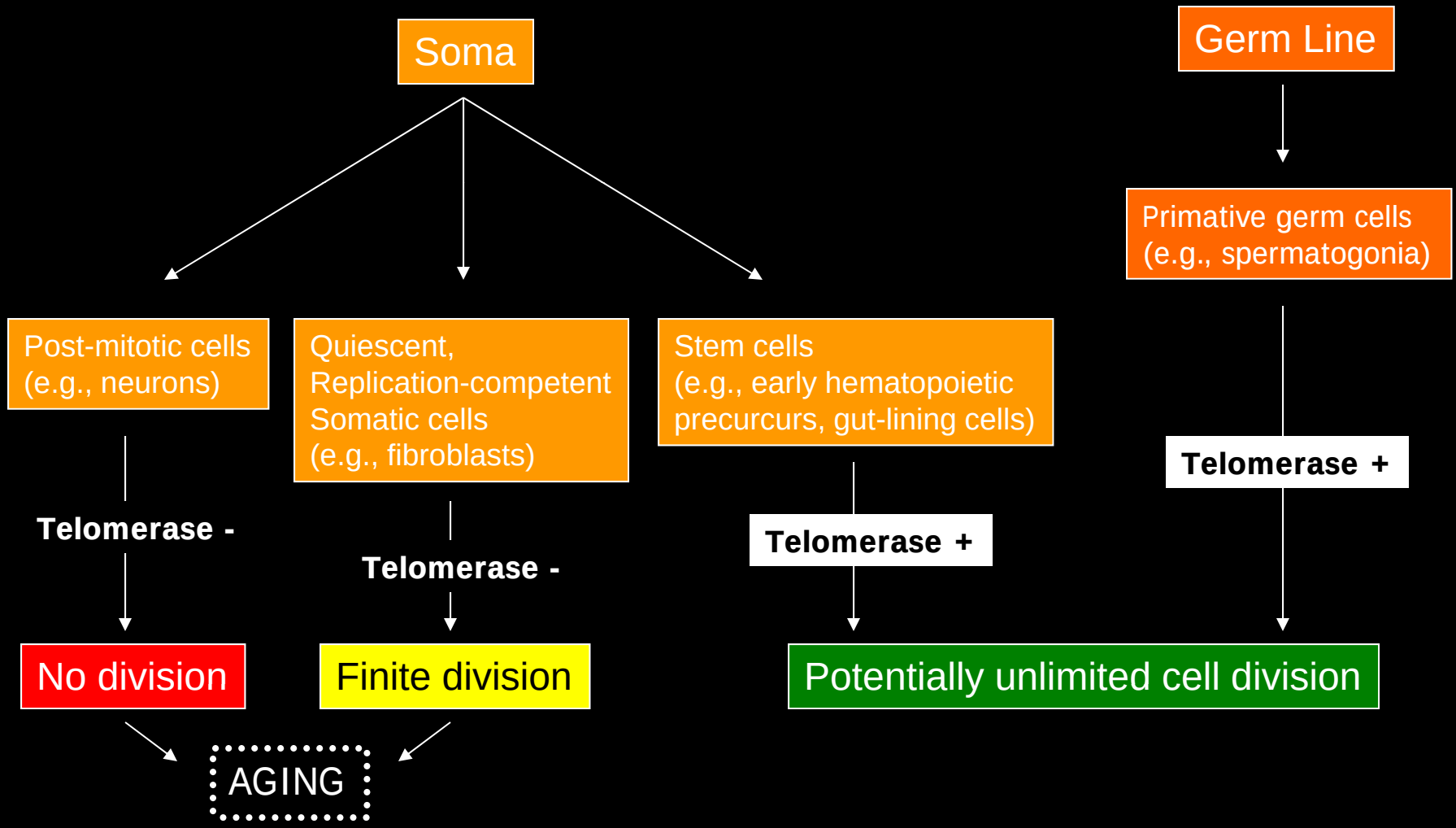
Aging in Telomerase-deficient Humans

Organ system	Cells expressing telomerase	Defect in dyskeratosis congenita
Hair	Hair follicle	Alopecia
Oral cavity	Squamous epithelium	Leukoplakia (precancerous oral lesions)
Skin	Basal layer of epidermis	Abnormal pigmentation Nail dystrophy
Lungs	Type 2 alveolar epithelial cells	Fibrosis
Liver	?	Cirrhosis
Intestine	Intestinal crypts	Gut disorders
Testes	Spermatogonia	Hypogonadism
Bone marrow	Progenitor stem cells	Failure to produce blood cells



Marciniak, R & Guarente, L Nature 413: 370-3 (2001).

Replication Potential of Normal Human Cells



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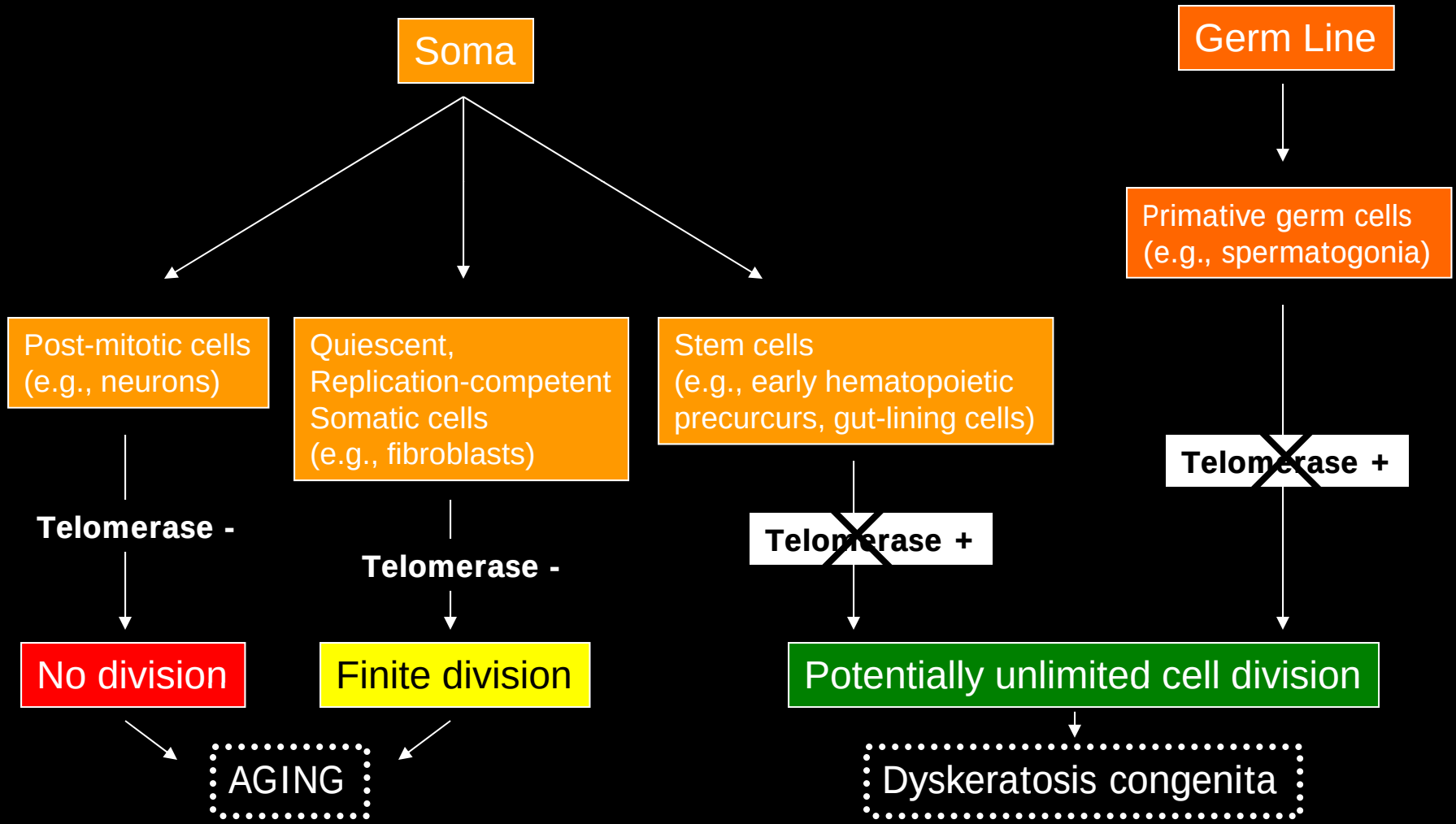
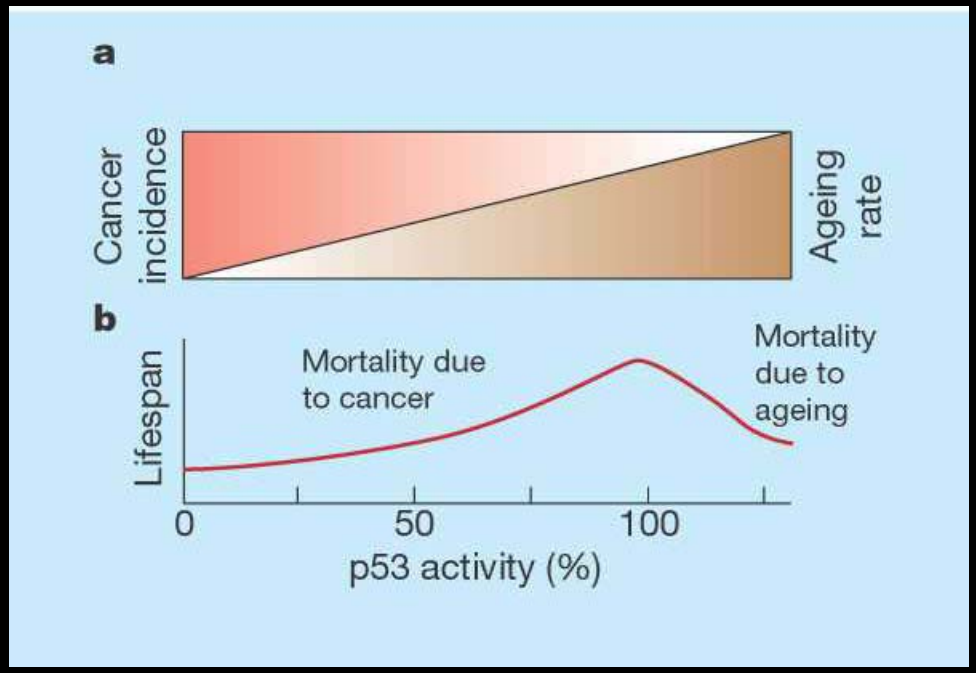
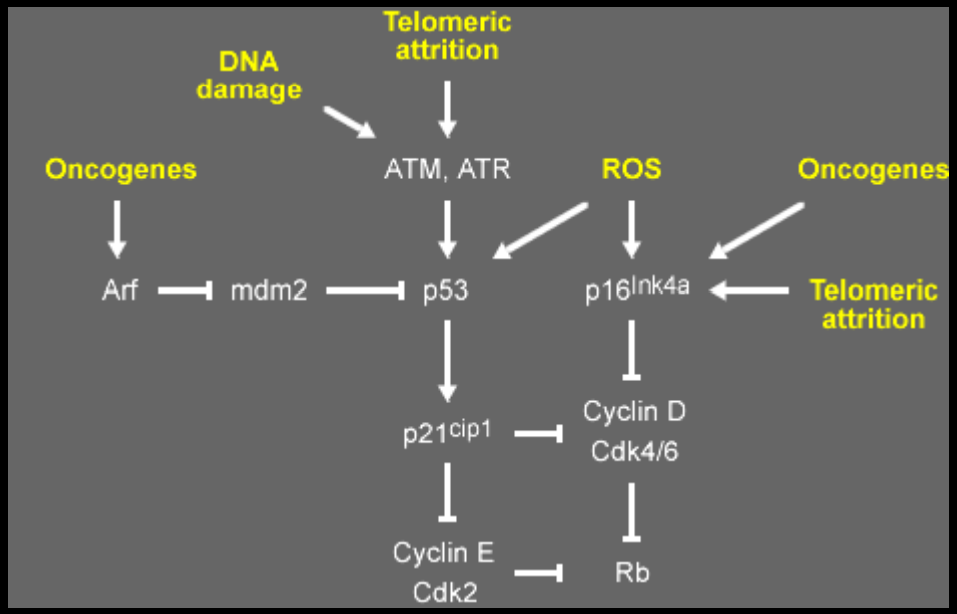


Aging, Cancer, and p53



Ferbeyre, G & Lowe, SW Nature 415: 26-7 (2002).

Interactions between p53/p21 and p16/Rb



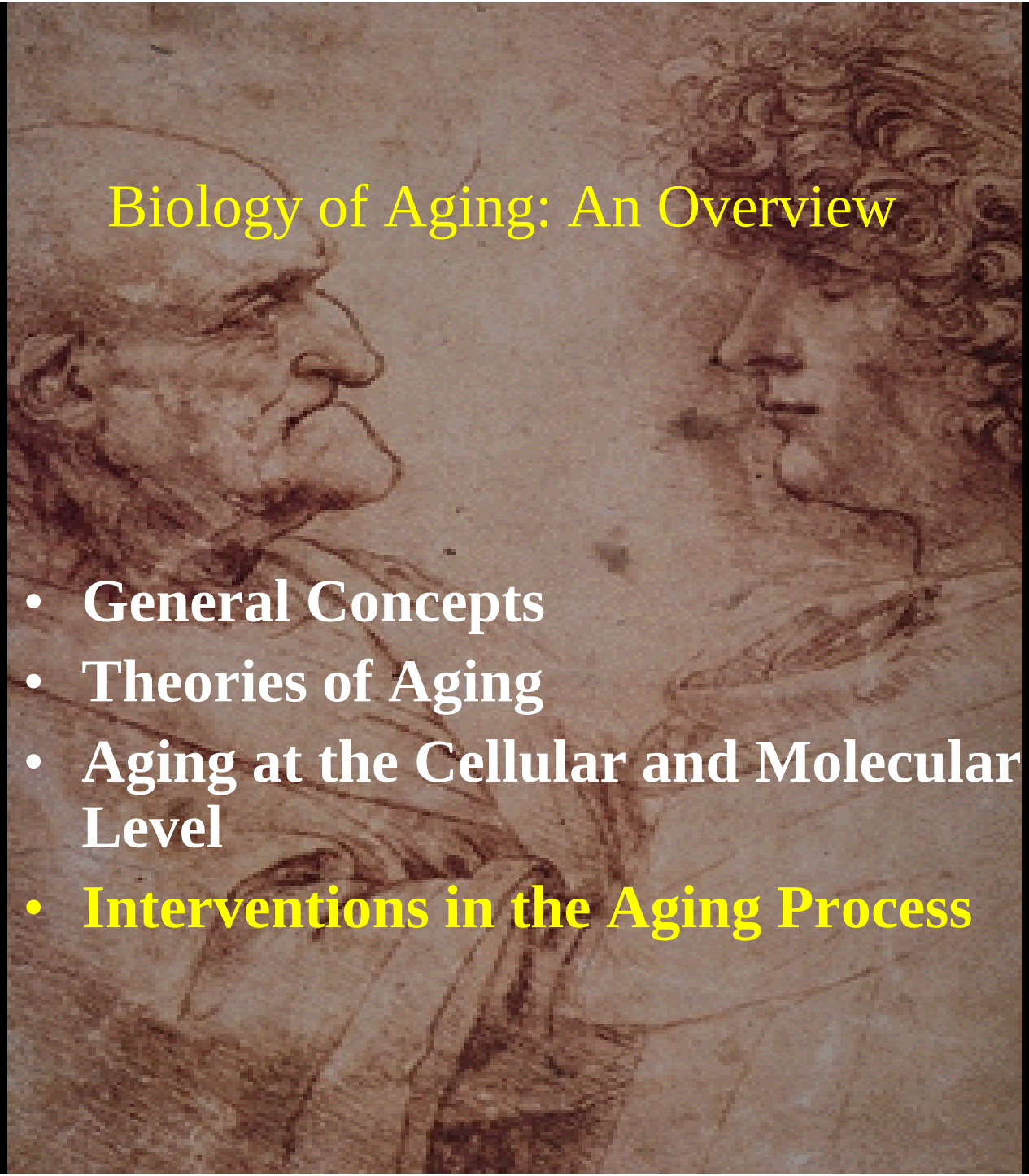
Q: Which one of the following statements most accurately describes immune senescence?

- It is associated with altered production of inflammatory cytokines.
- There is an increase in T and B cell diversity with age.
- It is similar in humans and mice.
- T memory cells decrease and T naïve cells increase with age.
- With aging, the response to new antigens remains intact.

Immune Senescence

(Perturbation of adaptive immune system with age)

- Altered/diminished immune responsiveness
  - Decreased response to new antigens
  - Decreased vaccine efficiency (e.g., influenza)
  - Compromised immune surveillance (?)
- Altered immune system physiology
  - Thymic involution
  - Decreased production of lymphocytes
  - Inversion in proportional representation of memory vs naïve cells (T memory cells increase and T naïve cells decrease with age)
- Altered immunoregulation
  - Increase in autoimmune syndromes (SLE, RA, SS, others)
  - Oligoclonal expansion of T- and B-cells (decrease in diversity with age)
  - Monoclonal gammopathies



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Interventions in the Aging Process

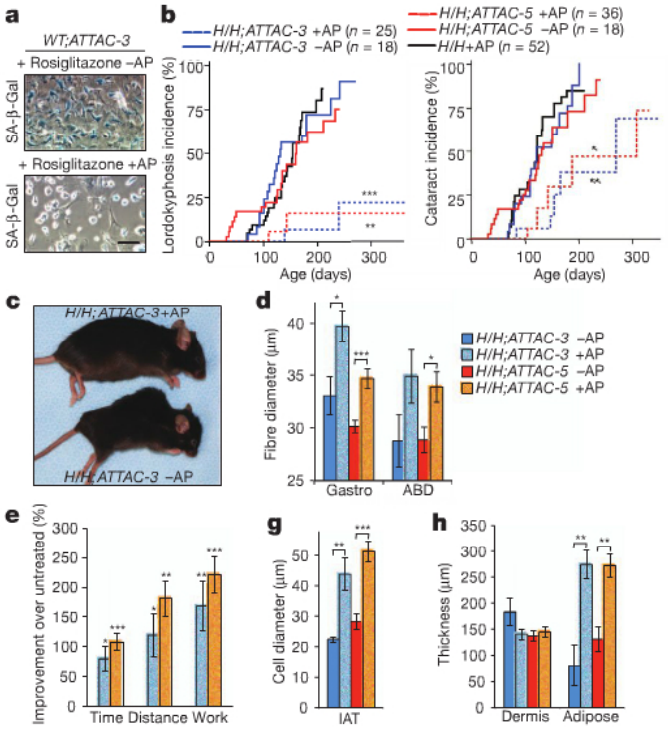
- Cell-based therapies
- Hormonal therapies
- Genetic manipulations
- Dietary therapies
- Other: hypothermia, exercise

LETTER

doi:10.1038/nature10600

Clearance of p16^{Ink4a}-positive senescent cells delays ageing-associated disorders

Darren J. Baker[1,2,3], Tobias Wijshake[1,4], Tamar Tchkonia[3], Nathan K. LeBrasseur[3,5], Bennett G. Childs[1], Bart van de Sluis[4], James L. Kirkland[3] & Jan M. van Deursen[1,2,3]



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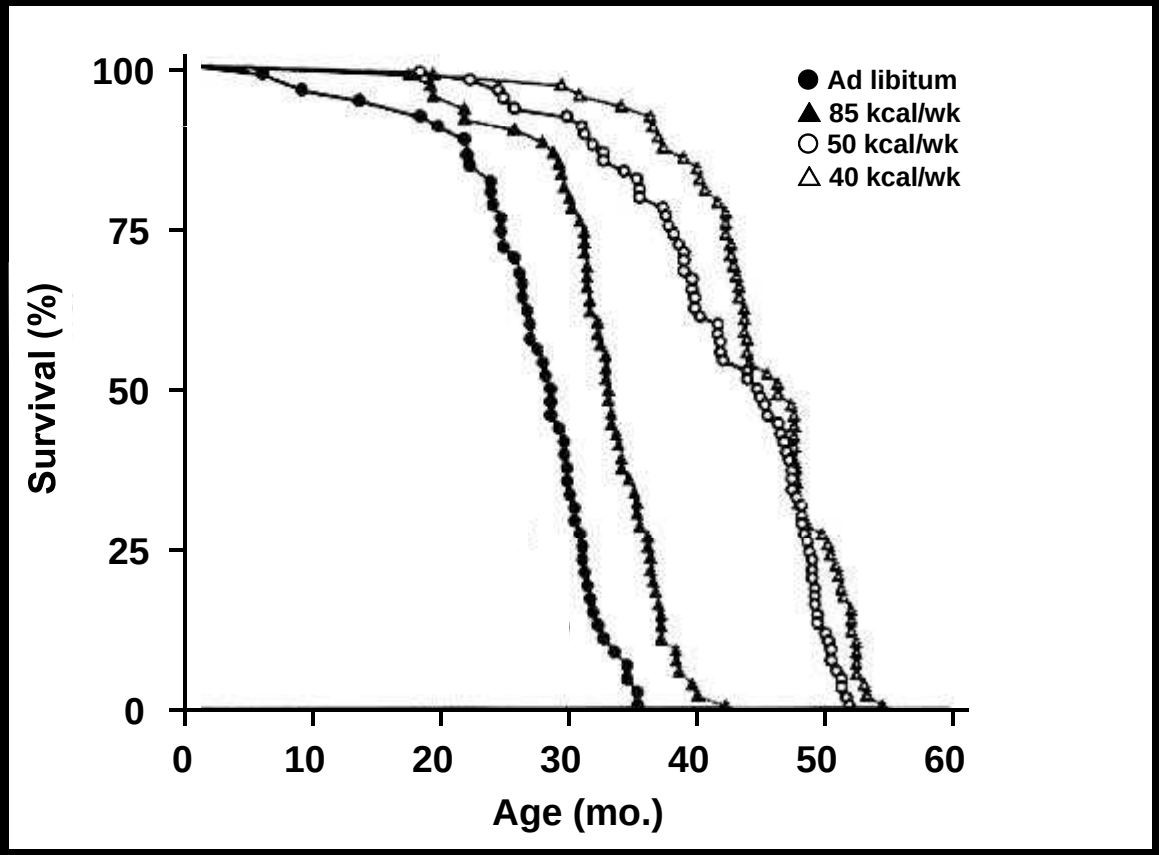
Mouse (treatment)	Weight (g)	Fat (%)	POV (g)	Peri (g)	IAT (g)	Mes (g)	SSAT (g)	Brown (g)
H/H;ATTAC-3 (–AP)	17.4 (1.8)	15.6 (3.4)	0.054 (0.05)	0.016 (0.02)	0.058 (0.02)	0.063 (0.05)	0.038 (0.01)	0.084 (0.005)
H/H;ATTAC-3 (+AP)	21.3* (3.8)	28.6*** (4.1)	0.334* (0.28)	0.069 (0.06)	0.192* (0.12)	0.151 (0.09)	0.095** (0.03)	0.119 (0.053)
H/H;ATTAC-5 (–AP)	16.7 (2.2)	15.4 (2.5)	0.137 (0.13)	0.020 (0.01)	0.075 (0.05)	0.061 (0.04)	0.050 (0.02)	0.104 (0.030)
H/H;ATTAC-5 (+AP)	24.0*** (2.1)	27.4*** (4.2)	0.433** (0.11)	0.071** (0.02)	0.225** (0.10)	0.262* (0.17)	0.115* (0.06)	0.159** (0.029)

Dietary Therapies

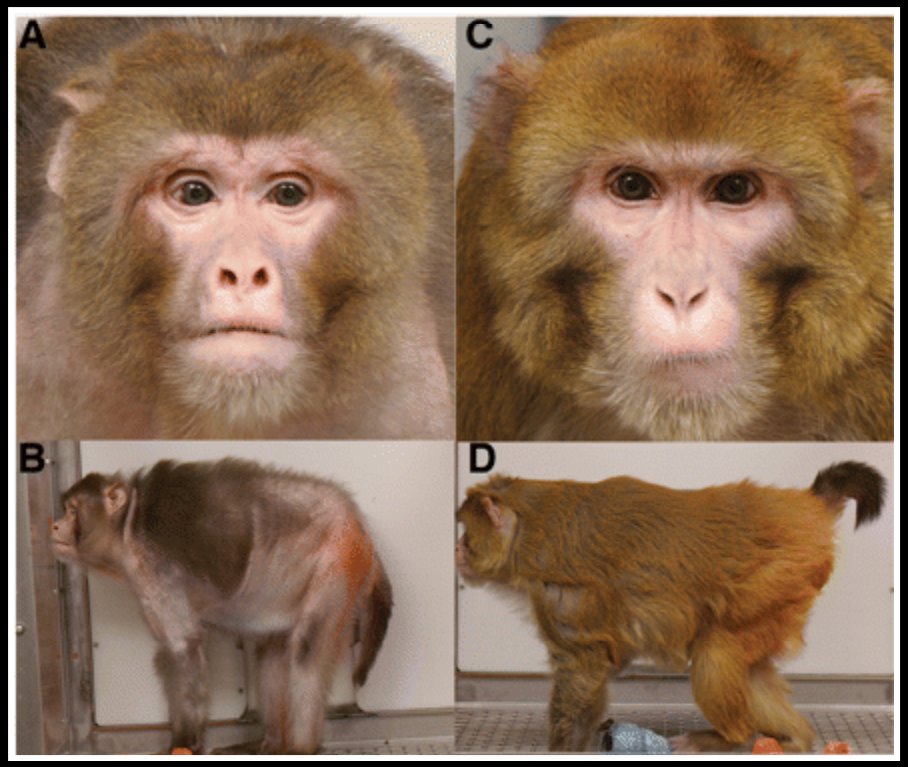
- Caloric Restriction
  - Extends average and maximum life spans by 30-40% if initiated in early adulthood, and by 20% if started in early middle age
  - Usually 30-60% reduction in calories with adequate content of essential nutrients
  - Effect preserved in a variety of species, including rodents, fish, flies, and worms

Effect of Dietary Restriction on Life Span



Weindruch, R & Sohal, RS NEJM 337: 986-94 (1997).

Caloric Restriction in Non-human Primates



A&B, 27 year old control; C&D, 27 year old CR

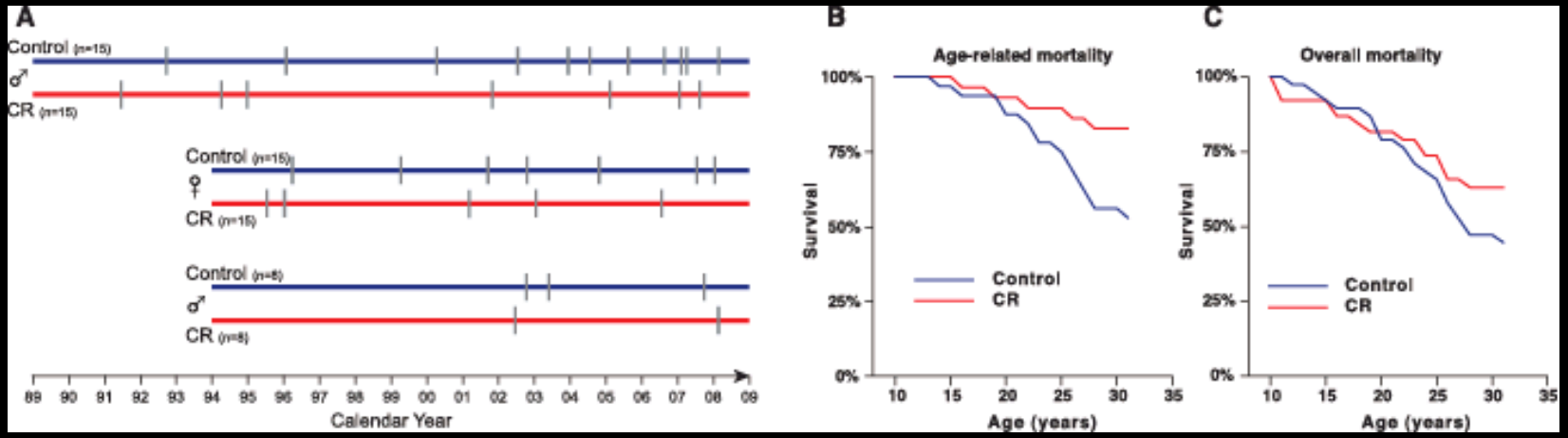
Caloric Restriction in Non-human Primates

- Altered Growth, Development or Metabolism
  - Lower body temperatures
  - Later sexual development
  - Later skeletal maturation
- Improved Health
  - Lower weight
  - Less abdominal fat

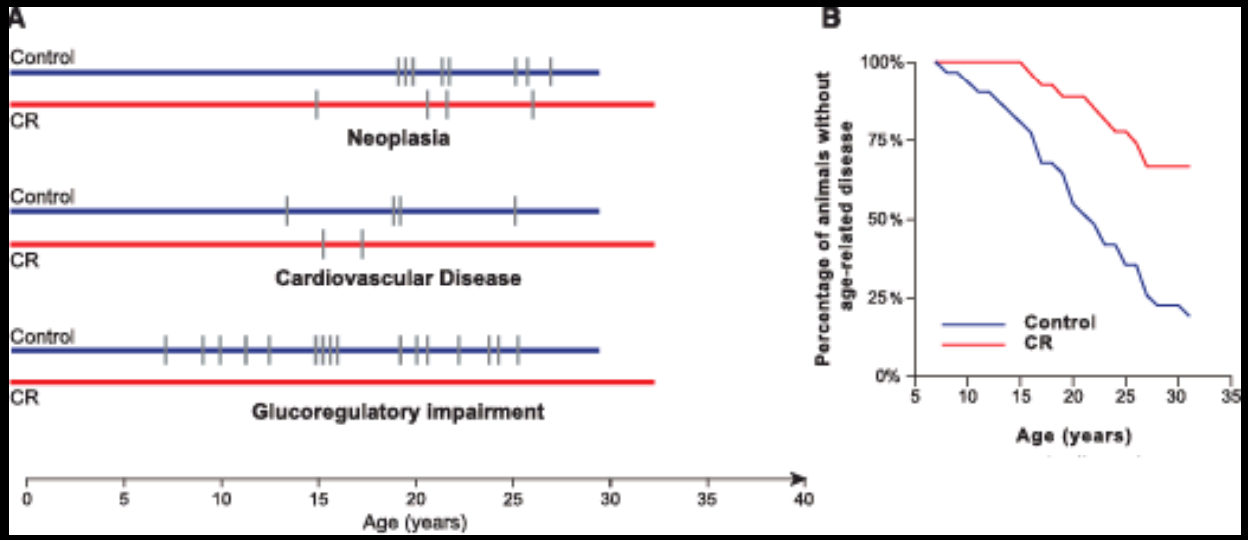
Caloric Restriction in Non-human Primates

- Reduced Risk for Age-related Diseases
  - Greater insulin sensitivity
  - Lower fasting insulin and glucose levels
  - Lower cholesterol and triglyceride levels
  - Higher HDL levels
  - Lower IGF-I levels
  - Slower decline in DHEAS
- Effects in Rodents but Still under Investigation in Monkeys
  - Later onset of age-related diseases (including cancer)
  - Longer average life span
  - Longer maximum life span

Caloric Restriction in Non-human Primates



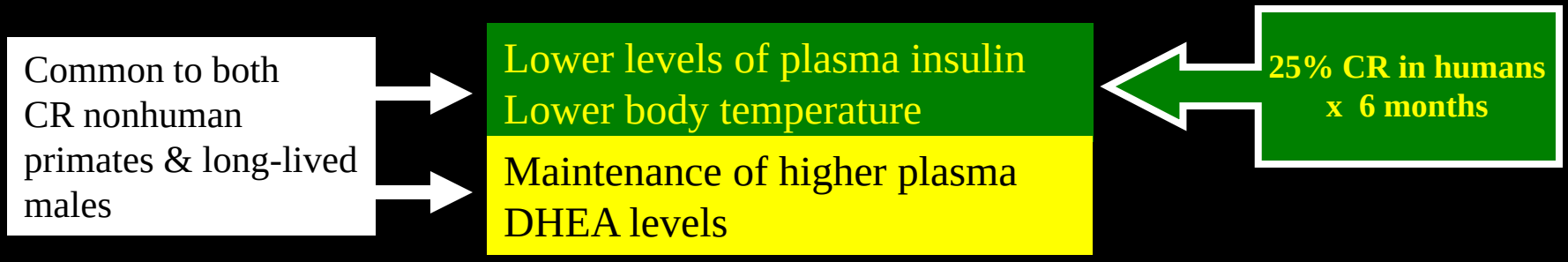
Caloric Restriction in Non-human Primates



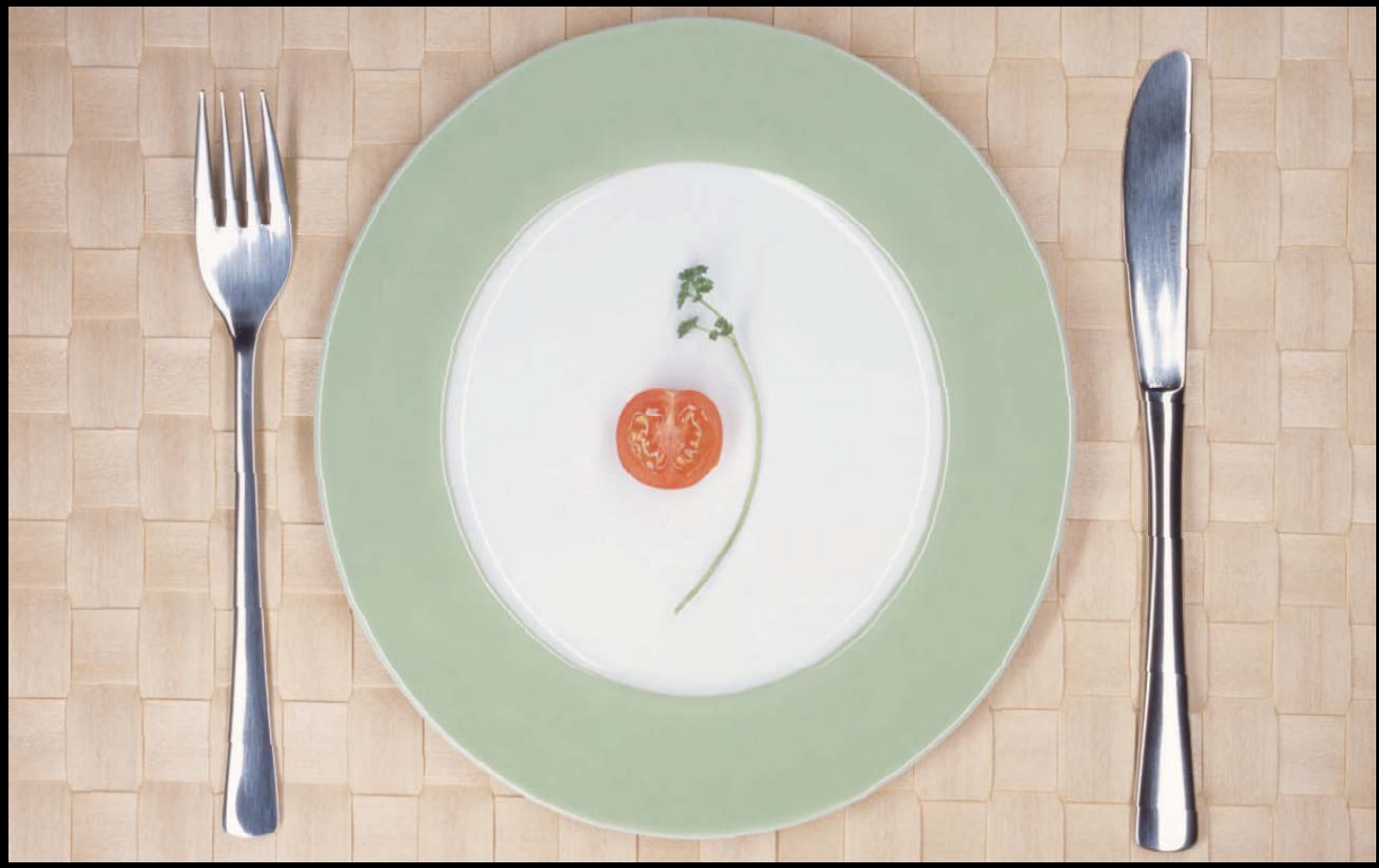
Caloric Restriction in Humans

- Okinawans
- Biosphere 2 Project
- Short-term studies in humans

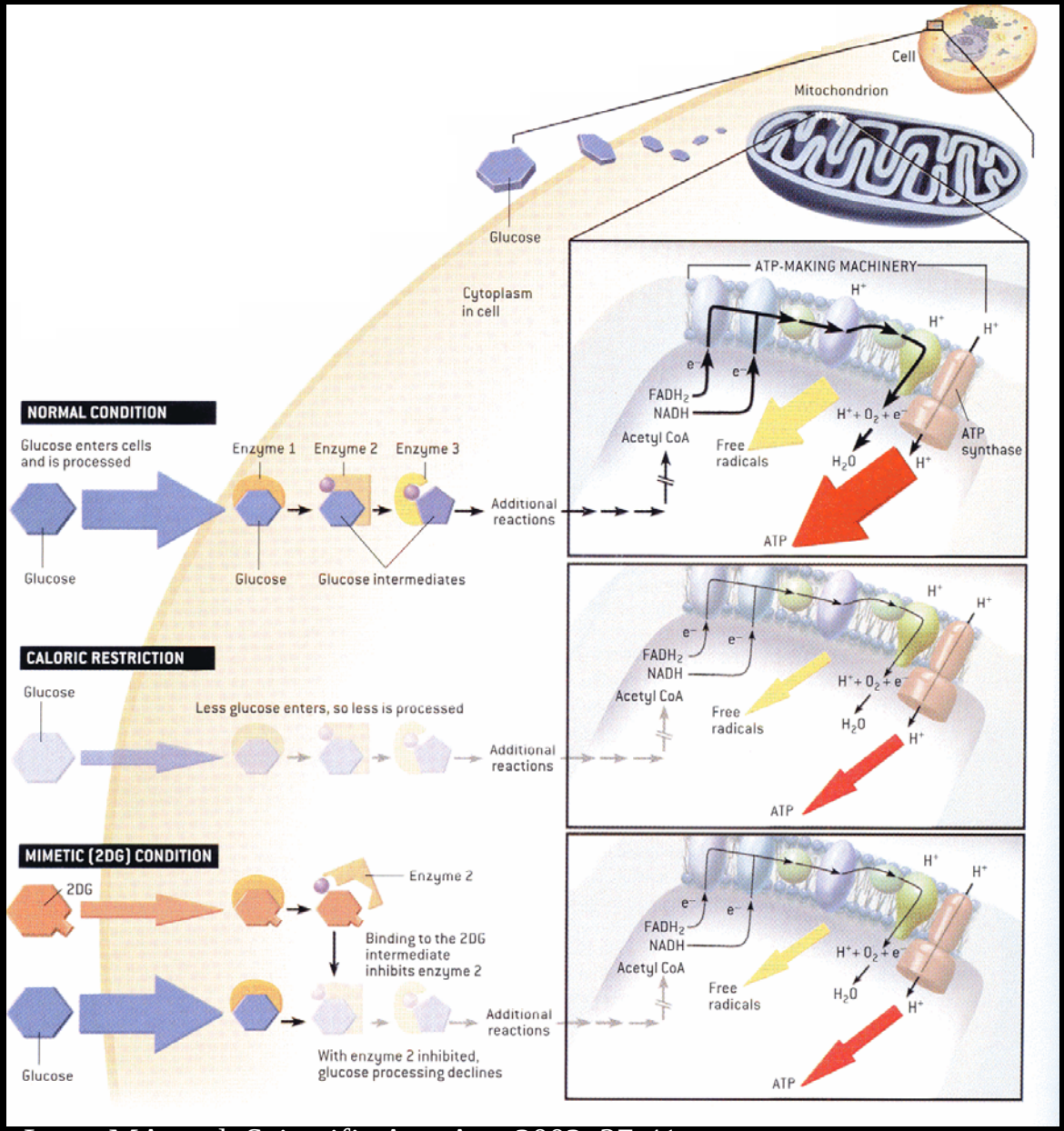
Caloric Restriction in Humans



Roth, GS er al. Science 305:1423-6 (2004)

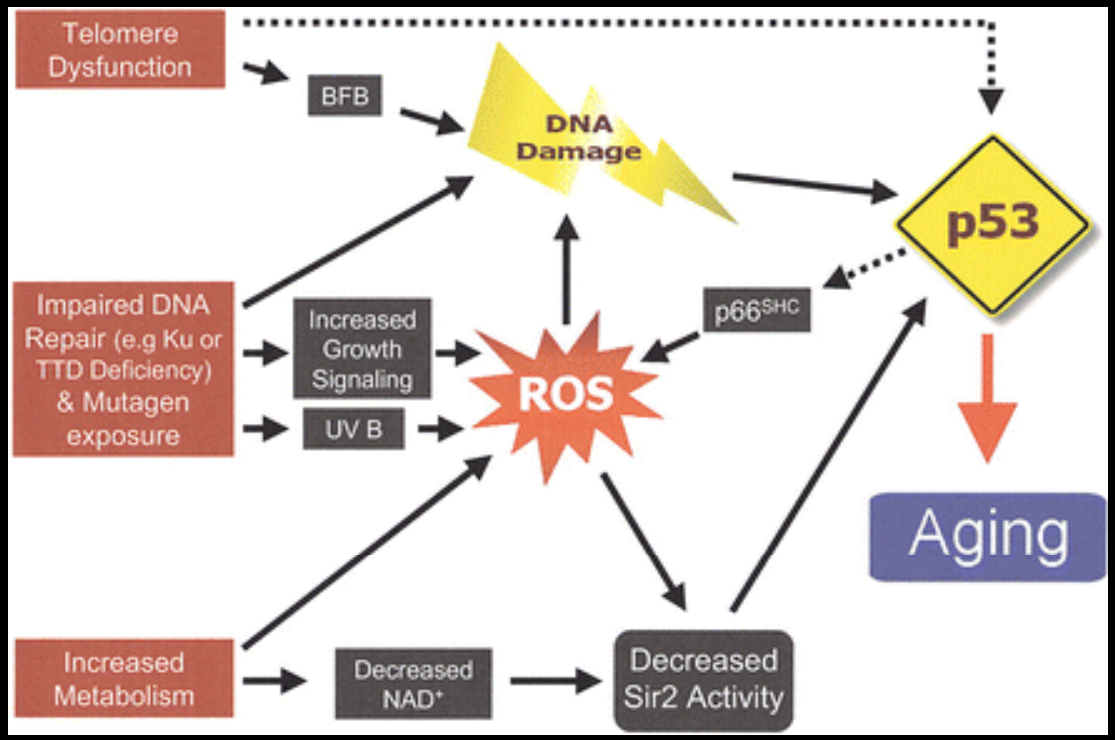


Prototype Caloric-Restriction Mimetic

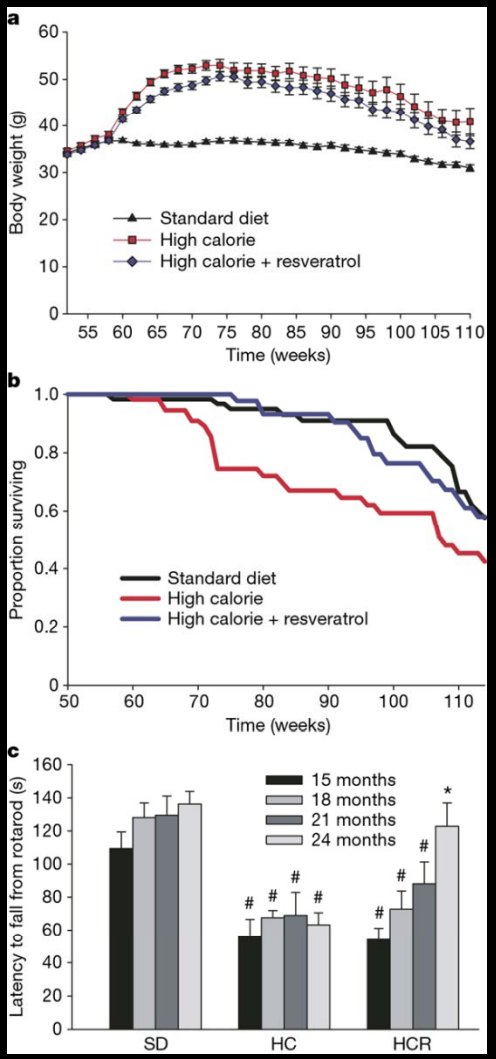


Lane, MA et al. Scientific Am. Aug 2002, 37-41.

Sirtuins (protein deacetylases): mediators of caloric restriction ?



Resveratrol, a sirtuin activator, improves health and survival of mice on a high-calorie diet



Baur, JA et al. Nature 444:337-42 (2006)

Effects of resveratrol

- Extends lifespan of diverse lower species:
  - S. Cerevisiae
  - C. elegans
  - D. melanogaster
- Changes parameters associated with longer lifespan:
  - Increased insulin sensitivity
  - Reduced IGF-I levels
  - Increased mitochondrial number
  - Improved motor function

Dietary Therapies

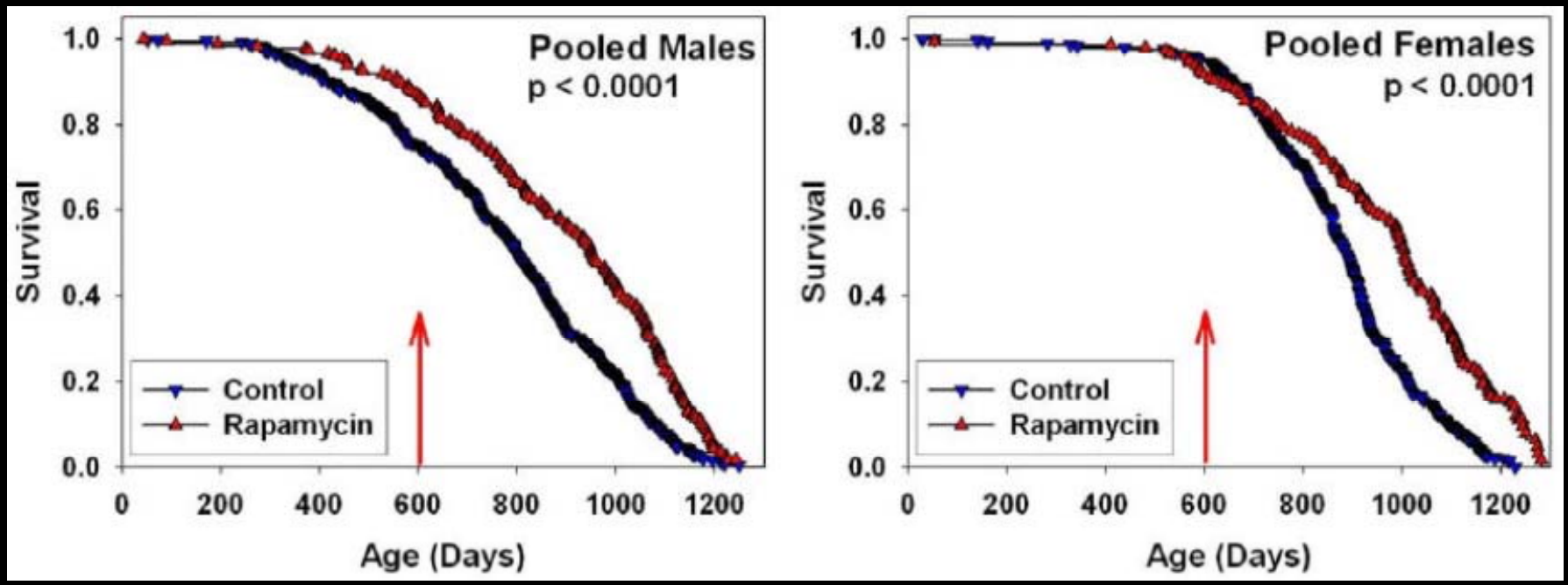
- Antioxidant supplementation
  - Does not significantly change median or maximum life span
  - Except for vitamin E (and possibly vitamin C) being able to lower lipid oxidative damage, no evidence to support reduction in oxidative damage in humans
  - A compound with catalase and SOD activities (EUK-134) extends longevity in nematodes
  - Foods with a high oxygen radical absorbance capacity (ORAC) may be more protective than other antioxidant preparations
  - Antioxidants may help reduce the incidence of ARMD

Butler, RN et al. J. Gerontol. 57A: B333-8 (2002).

Pharmaceuticals that have potential to extend life span

- National Institute of Aging has organized a multi-site study of in genetically heterogenous mice
- Of the agents being tested, aspirin and nordihydroguaiaretic acid have been found to lead to significant increases in life span in males
- Rapamycin leads to an increase in maximum longevity in both males and females
- Other compounds currently being tested as part of this initiative can be found at http://www.nia.nih.gov/ResearchInformation/ScientificResources/CompoundsInTesting.htm.

Rapamycin extends lifespan



Rapamycin:

-- extended median and maximal lifespan of both male and female mice

-- led to an increase in lifespan of 14% for females and 9% for males

-- reproducible extended life span at three independent test sites in genetically heterogeneous mice

-- did not affect disease patterns compared to control mice

Harrison DE et al., Nature 2009

Other dietary manipulations that extend maximum life span

- Low-methionine diets
- Brief, but early nutritional deprivation

Strong, R et all, Aging Cell (2009)
Sun, L et al., J. Gerontol. (2009)