## *Theories of Aging and Strategies to promote Healthy Aging*

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**Seminar for Vermont Medical College 2003**
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***Why do we age? What are good anti-aging interventions?***

## Maximum Life-span
## Mean Life-Span

- Mean life-span **(MLS)** is the average life-span age of a cohort studied. Often influenced by the environment, disease, and life-style
- Maximum life-span potential is the maximum age of one individual within a cohort studied. Mostly genetically determined (MLSP)

## What is Aging?


**Aging:**
Progressive

Universal

Post-maturation

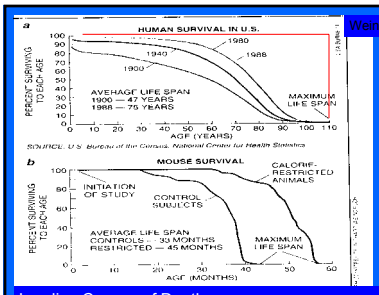
Irreversible?

**Senescence:**
Deleterious Aging

**Age-related diseases:** are the clinical manifestations of senescence

## General Objectives

- What is the objective of **The National Institute on Aging** and various groups investigating mechanisms of aging and strategies for healthy aging.
  - Improved understanding of the mechanisms of longevity can be used to fight age-related diseases and disabilities to ensure a healthy, active, and independent life well into very old age

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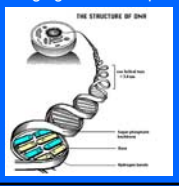
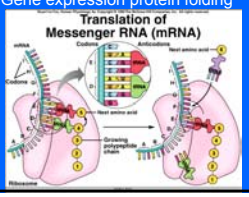
Leading Causes of Death

| **1900;** | **2003;** |
|---|---|
| 1) pneumonia, tuberculosis | 1) heart disease |
| 2) GI infections, diarrhea | 2) cancer |
| 3) heart disease | 3) neurodegenerative diseases |
| | 4) sarcopenia related injury |

## Molecular Gene Theories

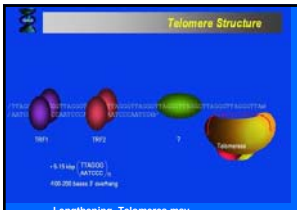
- Codon restriction - Fidelity/accuracy of mRNA translation is impaired due to inability to **decode codons** in mRNA.
- Error catastrophe - Fidelity of **gene expression** declines with age, resulting in increased fraction **of abnormal proteins**.
- Somatic mutation - Accumulation of **molecular damage**, primarily to DNA/genetic material.
- Dysdifferentiation - Gradual accumulation of **random molecular damage** impairs regulation of gene expression.
- Gene regulation - Aging caused by **changes in gene expression** regulating both aging and development. Gene expression protein folding and activity



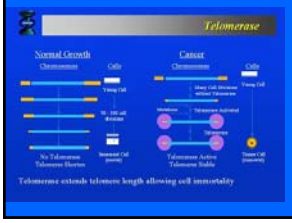


# Cellular Theories

- Free radical - Oxidative metabolism produces highly reactive free radicals that subsequently damage protein and DNA. Mitochondrial DNA Damage (Mitochondrial Theory of Aging)
- Wear and tear - Accumulation of normal injury
  - Inflammation Theory of Aging
  - Glycoxidation Theory of Aging (products from glucose with proteins + oxidation; AGE (advanced glycation End-products
- Apoptosis - Programmed cell death resulting from intrinsic damage and genetically determined events or genome crisis.
- Senescence - Phenotypes of aging are caused by an increase in frequency of senescent cells. Senescence may be the result of telomere loss (replicative senescence) or cell stress (cellular senescence).

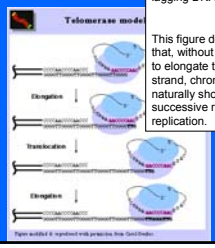


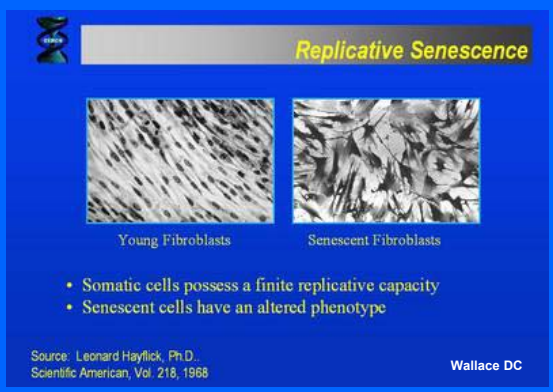

Lengthening Telomeres may increase the risk for cancer




Telemetries, a reverse transcriptase, extends the lagging DNA strand.

This figure demonstrates that, without a mechanism to elongate the lagging strand, chromosomes will naturally shorten with each successive round of DNA replication.

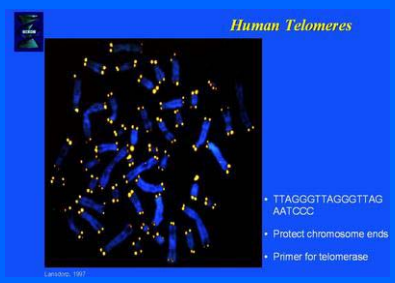



# System Theories

- Rate-of-living - Assumes a fixed amount of metabolic potential for every living organism (live fast, die young).
- Neuroendocrine - Alterations in neuroendocrine control of homeostasis results in age-related physiological changes. Neuroendocrine Theories of Aging
- Immunologic – Well documented decline of immune function with age results in increased incidence of disease. Immunological Theory of Aging

# Telomeres (+ enzyme Telomerase)




# Evolutionary Theories

- Disposable Soma - Somatic cells are maintained only to ensure continued reproductive success, following reproduction the soma is disposable. (life span theory)
- Antagonistic Pleiotropy - Genes that are beneficial at younger ages are deleterious at older ages.
- Mutation Accumulation - Mutations that affect health at older ages are not selected against.

# Opossums

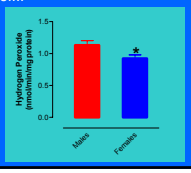
- Mainland Opossums
- - ~80% die from predators in the first year; typically reproduce only once; Age very rapidly
- Sapelo Island Opossums
- - out in daylight (no predators)
- - reproduce twice (fewer offspring/litter)
- - longer average life span
- *Sapelo island opossums live longer because they age more slowly than mainland opossums. Demonstrated by reduced levels of collagen cross-linking in Sapelo island opossums when compared to mainland opossums. (Collagen X-linking measures the amount of molecular damage accumulated over time)

## Very Long-lived Species; Maximum Life-span, Mean Life-span, Species-Specific Differences

Humans (~77-M ~80-F years) Maximum ~122y

Moreover most centenarians are females!!!!

Elephants
70 Years in the wild (~10y Zoo)




## There are clear Species-Specific Differences in Maximum Life-span.

### Short-lived Species

***Caenorhabditis Elegans***

(14-21 Days)

*Drosophila Melanogaster*

(1-3 Months)

*Rattus* (2-3 Years)

Fischer-344

Jeanne Calment 122 Years February 21,1875 August 4,1997

**Jeanne Louise Calment** was born in Arles, France on February 21, 1875. She once met Vincent Van Gogh in her father's shop. Her genes may have contributed to her longevity as **her father lived to the age of 94** and her **mother to the age of 86**. She married a distant cousin at the age of 21. Her only grandson died in 1963. **She rode a bicycle to the age of 100.**

## Long-lived Species; Maximum Life-span, Mean Life-span, Species-Specific Differences.

Monkeys

(20-30 years)

Homology 98.7%

Is the difference in the 1.3%?

Bats (10-30 years) High Metabolism, but long life-span and maybe a reduced radical production?

## Proteonomics; Protein Expression and Folding:

W. Enard et al., "Intra- and interspecific variation in primate gene expression patterns," *Science*, 296:340-3, April 2002.

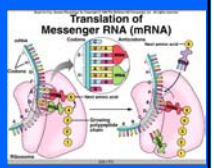
**-Although humans and chimpanzees are 98.7% genetically similar.....**

**-Investigators have taken genomics one step further by using DNA microarrays to measure the expression levels (that is, mRNA levels) in the liver and brain of humans and chimpanzee.**

**-The distance between one of the human samples and the others is greater than the overall distance between humans and chimpanzees,.....**

**Altered gene expression could explain the genetic difference between human and chimp and could therefore provide and alternative explanation for life-expectancy differences within humans and between primates and humans.**

Monkeys (20-30 years)
Homology 98.7% with Humans
Is the difference in the 1.3%?



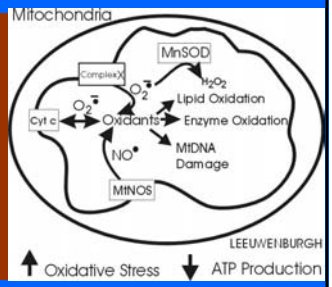
# The Free Radical Theory of Aging

Oxygen free radicals generated cause cumulative oxidative damage, resulting in structural degeneration (extra cellular material, protein aggregation, apoptosis, etc.) functional decline, and age-related diseases.

Some believe that oxidative stress is the predominant cause of age-associated degenerative change.

# Mitochondrial Dysfunction and Aging
## Mitochondrial Theory of Aging

- ⇑ Oxidative stress
- ⇑ mt-DNA damage
- ⇑ mt-DNA deletions
- ⇑ Oxidized proteins
- ⇑ Lipid peroxidation
- ⇑ Lipid-adduct formation
- ⇓ Decrease in repair systems




•First some basic questions?

- What are free radicals or better named oxidants?
- Where are these oxidants produced?
- What type of oxidants are produced?

# Radical Reactions

$O_2 + e <=> O_2^{\bullet-}$ Equation 1

$O_2 + 2e + 2H^+ \rightarrow H_2O_2$ Equation 2

$O_2^{\bullet-} + O_2^{\bullet-} + 2H^+ \rightarrow SOD \rightarrow H_2O_2 + O_2$ Equation 3

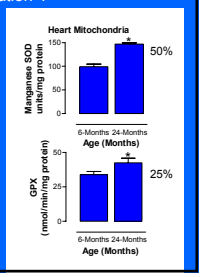
$H_2O_2 + 2GSH \rightarrow GPX \rightarrow H_2O + GSSG + ROH$ Equation 4

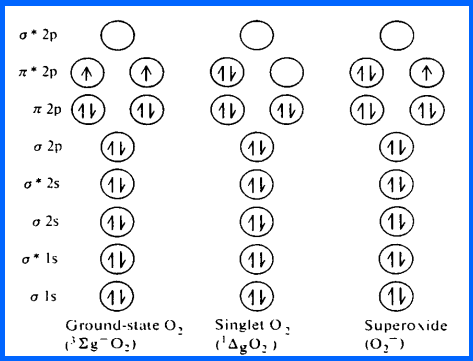
$2H_2O_2 + \rightarrow Catalase \rightarrow 2H_2O + O_2$ Equation 5

$Fe^{2+} + H_2O_2 \rightarrow HO^{\bullet} + HO^- + Fe^{3+}$ Equation 6

$O_2^{\bullet-} + NO^{\bullet} \rightarrow ONOO^-$ Equation 7

$O_2^{\bullet-} + M^{n+} \rightarrow O_2 + M^{(n-1)+}$ Equation 8



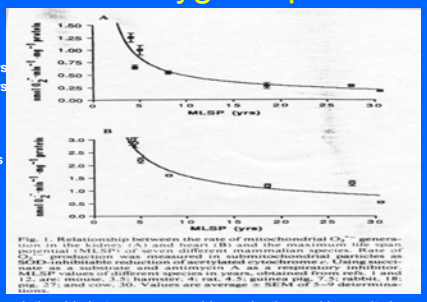




•**Aging** selectively decreases the rate of oxidative phosphorylation in the interfibrillar population of cardiac mitochondria (IFM) located among the myofibers, whereas subsarcolemmal mitochondria (SSM) located beneath the plasma membrane remain unaffected. **Lesnefsky EJ, Gudz TI, Moghaddas S, Migita CT, Ikeda-Saito M, Turkaly PJ, Hoppel CL. Mol Cell Cardiol. 2001 Jan;33(1):37-47**


Electron micrograph of the swimming muscle (longissimus dorsi) of a Harbor seal: white lines denote the cell membrane or the sarcolemma of three different muscle cells; the yellow arrows point at subsarcolemmal mitochondria; the white arrows point at the interfibrillar mitochondria and the blue arrows show a lipid droplet.

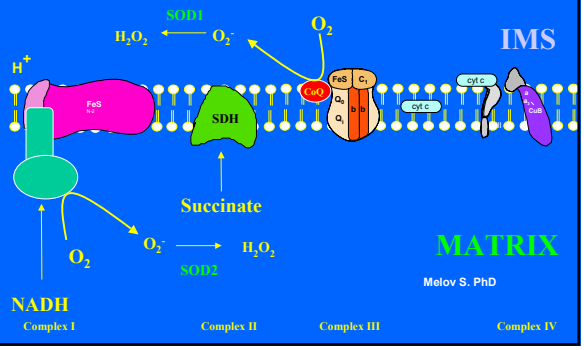
# Long-Lived Organisms Produce Less Reactive Oxygen Species

- Animals and MLSP
  - Mouse 3.5 years
  - Hamster 4 years
  - Rat 4.5 years
  - guinea pig 7.5 years
  - Rabbit 18 years
  - Pig 27 years
  - Cow 30 years



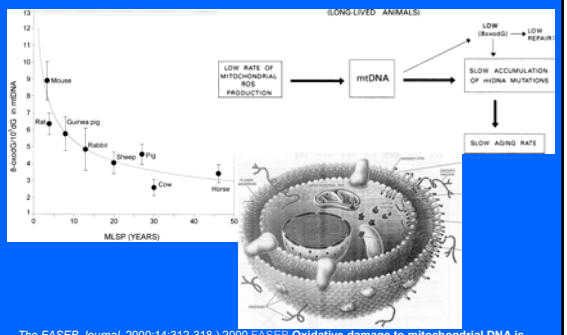

There is an inverse relationship between superoxide production and longevity in both insects and mammals (Ku et al. 1993)

# Reactive Oxygen species and the Respiratory Chain



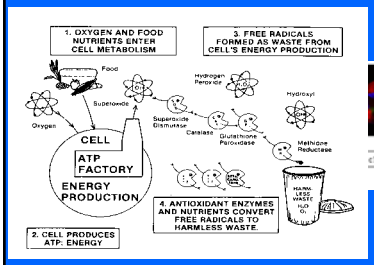

Melov S. PhD

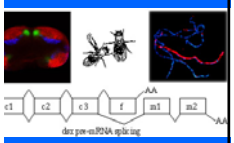
# Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals




*The FASEB Journal.* 2000;14:312-318.) 2000 FASEB **Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals GUSTAVO BARJA[1] and ASUNCIÓN HERRERO**

# Engineering of Genes to increase Antioxidant Defenses




-Fruit flies that over-express copper-zinc superoxide dismutase (SOD2) and catalase (the first line of defense against oxidative damage) show less oxidative damage to DNA and protein and live up to 34% longer than controls (Orr and Sohal, Science 1994)

# Long-lived Species; Maximum Life-span, Mean Life-span, Species-Specific Differences.

Bats (10-30 years) and Birds (30-100) have a high metabolism (similar to rats (2-4 years), but are long lived! A reduced radical production has been detected in these long-lived species.(" life fast die young")

What is important is the production of mitochondrial oxidants (ROS) and not $O_2$ consumption. (In general it correlates negatively with MLSP).

# Genetic Engineering has not worked in Longer-lived species

Ubiquitous Overexpression of CuZn Superoxide Dismutase Does Not Extend Life Span in Mice

Ting-Ting Huang, Elaine J. Carlson, Anne Marie Gillespie, Yuping Shi, and Charles J. Epstein

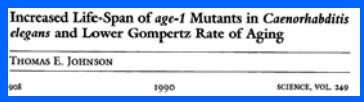
# Oxidative Stress and Aging

- What happens when oxidant production is greater then antioxidant defenses?
  - **Oxidative Stress**
    - DNA damage
    - Protein damage
    - Lipid Damage

## *Increasing life-span in C. Elegans and Drosophila Melanogaster*

**Studies in invertebrates have led to the identification of a number of genes that regulate lifespan, some of which encode components of the insulin or insulin-like signaling pathways.**

**Examples include the related tyrosine kinase receptors InR** (Drosophila melanogaster) **and DAF-2** (Caenorhabditis elegans) **that are homologues of the mammalian insulin-like growth factor type 1 receptor (IGF-1R).**



Increased Life-Span of *age-1* Mutants in *Caenorhabditis elegans* and Lower Gompertz Rate of Aging

THOMAS E. JOHNSON

908 1990 SCIENCE, VOL. 249

Mutations in certain genes in the *C. elegans* can also increase life span. For example daf-2 controls *dauer* formation, a metabolic slowed, non-aging state. This occurs naturally when food is limited or there is overcrowding.

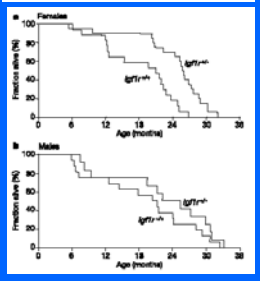
Mutations cause an 3- 4-fold increases of life span.

# Free Radical Theory

- **- Oxidative metabolism produces highly reactive free radicals that subsequently damage protein and DNA.**
- Evidence from model organisms...
- - Superoxide dismutase (SOD) transgenes can extend the life span of *Drosophila.*
- - Chemicals that mimic catalase (peroxidase) activity can extend *C. elegans* life span.
- - Long-lived mutants are typically stress resistant, including resistant to drugs (i.e. paraquat stress, which induces increases in free radicals)
- - Life span extension by insulin-like signaling mutants in *C. elegans* requires catalase activity.

**IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice**

Martin Holzenberger*, Joëlle Dupont†, Bertrand Ducos*, Patricia Leneuve*, Alain Géloën‡, Patrick C. Even§, Pascale Cervera‖ & Yves Le Bouc*



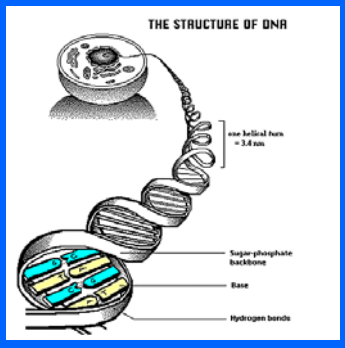

**-To investigate whether IGF-1R also controls longevity in mammals, these scientist inactivated the IGF-1R gene in mice (Igf1r).**

**-Here, using heterozygous knockout mice because null mutants are not viable, we report that Igf1r1/2 mice live on average 26% longer than their wild-type littermates ($P < 0.02$).**

**-The increase in life-span was only significant in the Females**

**Holzenberger, M., Dupont, J., Ducos, B., Leneuve, P., Geloen, A., Even, P. C., Cervera, P., and Le Bouc, Y. (2003) IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature* 421, 182-187**

# There are "Age" Genes



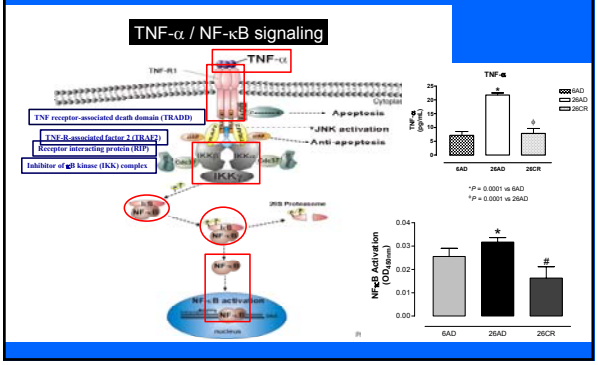

# Insulin-like signaling in *C. elegans*

- -Evidence for genetic regulation of life span.
- 1- Mutations that reduce insulin-like signaling can extend *C. elegans* lifespan - significantly.
- 2- A conserved transcription factor is required for life span extension, indicating a regulated genetic response to reduced insulin-like signaling.
- 3- Conserved in *Drosophila* and mouse.
  - Insulin levels rise when we consume food, and drop in the absence of food, because reducing insulin-like signaling in *C. elegans* extends life span scientist are investigating if calorie restriction extends life span by reducing insulin-like signaling, does it?

## Wear and tear - Accumulation of "normal" injury

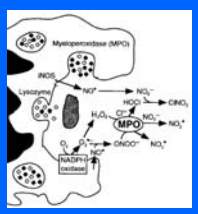
- Inflammation Theory of Aging
- Glycoxidation Theory of Aging (products from glucose with proteins + oxidation; AGE (advanced glycation End-products

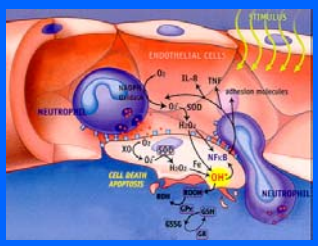
**The effects of age and calorie restriction on TNF-α / NF-κB signaling in skeletal muscle**




Sources of Oxidants

Chronic Inflammation and Oxidant Stress




## Inflammation theory of aging

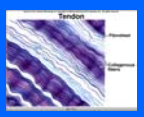
- The Molecular inflammation hypothesis of aging is based on specific anti-aging mechanism of calorie restriction, such as the reduction in **TNF-α / NF-κB signaling**

## Inflammation theory of aging

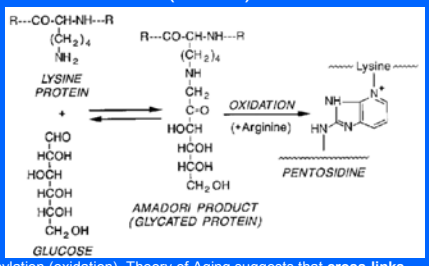
- **The inflammation theory of aging** goes hand-in-hand with the **free radical theory of aging** and the **glycooxidation theory of aging**

## Glycoxidation Theory of Aging

- Cooking and Browning Reaction
  - Cooking of foods accelerates the Browning or Maillard reaction
  - The toxic substances formed can lead to mutations and cancer



## Advanced Glycosylation End products (AGEs)




•The Glycosylation (oxidation). Theory of Aging suggests that **cross-links generated** in **proteins** and **nucleic acids** by **nonenzymatic glycosylation** may contribute to age-related declines in the functioning of cells and tissues.

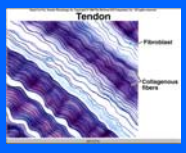
•Non-enzymatic addition of glucose to proteins may gradually slow down the protein function.

•Non-enzymatic addition of glucose to nucleic acids may gradually damage DNA.

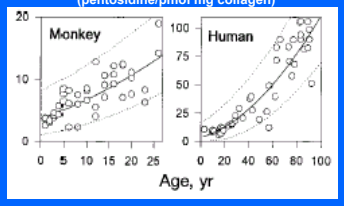
## Hormone Theories
## Decline in Estrogen and Testosterone

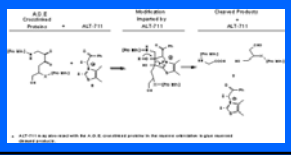
- ***DHEA*** dehydroepiandrosterone is secreted by the adrenal glands and called a master hormone because it is **converted into many other hormones involved in growth and strength.**
- Supplements of DHEA, which declines with age in both men and women, have been shown in animal studies to reverse many debilitating signs of aging
- Risks of cancer with long term use and risk for prostate cancer etc. unknown

**Longevity and the genetic determination of collagen glycoxidation kinetics in mammalian senescence. Sell et al. *PNAS*, 93, 485-490, 1996**




(pentosidine/pmol mg collagen)



ALT-711 = 3-phenacyl-4,5-dimethylthiazolium chloride

Melton. Age breakers. Rupturing the body's sugar-protein bonds might turn back the clock. Sci Am. 2000 Jul;283(1):16.

Kass et al. **Improved arterial compliance by a novel advanced glycation end-product cross-link breaker.** Circulation 2001 25;104(13):1464-70

## Immunological Theory of Aging (Decline in Function Resistance to Stress

- In general, **humoral immunity** declines with age, and the onset can occur as early as when an individual reaches sexual maturity
- Aging appears to **effect T cell number/function**
- Decline could lead to increase in **risk to viral infections and cancer.**
- Cell loss **(Apoptosis)** , shift in the proportion of sub-populations, and qualitative cellular changes have all been detected

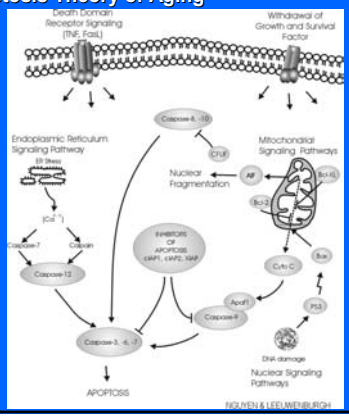
## Summary
## Glycooxidation

- Cross-linking sugar related to the aging process? Yes
- Thus the aging process is also governed by certain chemical molecules and structure formations that are likely to participate in reactions to "slow you down", which are not intended by genes

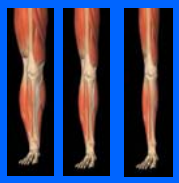
**Apoptosis Theory of Aging**

-Apoptosis (programmed cell death) could be activated "prematurely" in post-mitotic cells and contribute to the aging process.

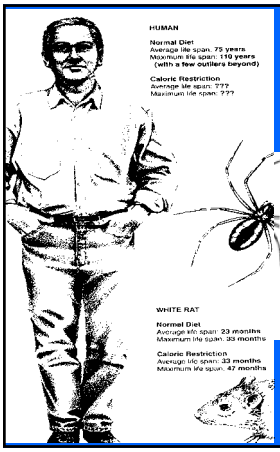
-What is the mechanism with age and what mechanisms can life-long exercise prevents the age-related loss in post-mitotic cells



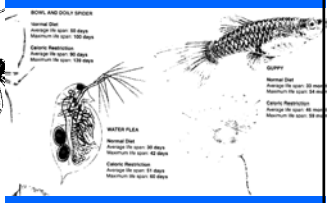
## Myocardial Aging, Sarcopenia, Neurodegeneration, Oxidative Stress and Apoptosis

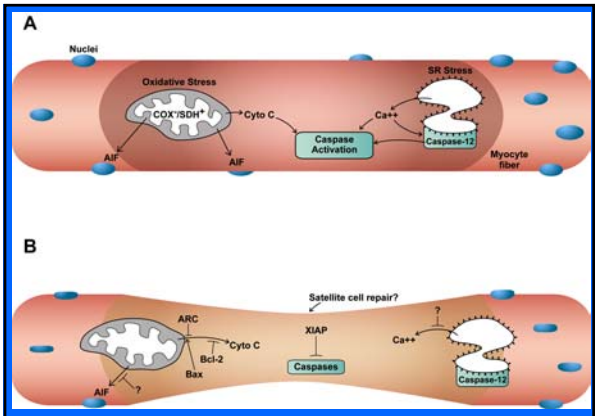


- ↓ in total number of skeletal and heart myocytes as well as neurons with age
- May lead to accelerated decline in cardiac functional capacity, sarcopenia, neurodegenerative diseases
- Oxidative Stress and Apoptosis may be one major factor



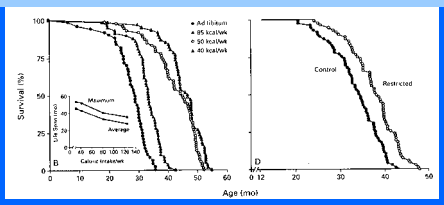

Reduction in Caloric Intake (~30-50%) **without malnutrition** Increases Mean and Maximum Life-span. Reduces tumors, renal disease and cardiomyopathy






Dirks and Leeuwenburgh; FRMB; In Press

**Aging and Caloric Restriction:** Reduction in caloric intake (~30-50%) without malnutrition increases mean and maximum life-span, reduces sarcopenia (skeletal muscle atrophy and cell number) and improves neuronal function.




Weindruch, N Engl J Med 1997; 337:986-994, Oct 2, 1997.

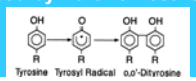
## Therapies-Strategies to promote Healthy Aging and to Prolong Life

- Interventions that may promote health and prolong maximum life-span:
  - Life-Long-Caloric Restriction
  - Life-Long-Exercises
  - Anti-inflammatory Compounds (Aspirin)
  - Antioxidant Therapies (flavonoids,etc)
- *Genetic Engineering and Organ Transplant*

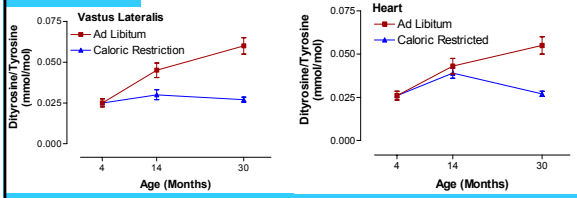
## Caloric Restriction

**-Reduces oxidant**
**-Reduces cytokines**
**-Reduces glycoxidation**
**-Reduces Pathology**

## Oxidative Damage in Skeletal Muscle is still increased with Aging and is Reduced by Caloric Restriction




Oxidative Stress



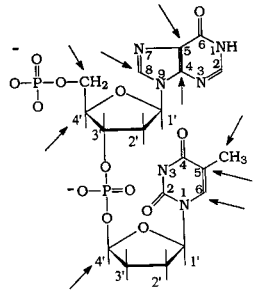

Leeuwenburgh, C., Wagner, P., Holloszy, J.O., Sohal, R.S., and Heinecke, J.W. 1997. Caloric restriction attenuates dityrosine cross-linking of cardiac and skeletal muscle proteins in aging mice. Arch Biochem Biophys 346:74-80.

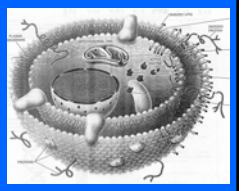
**Reduction of the Incidence of tumors following restriction of food intake**

| Treatment | Rodents | Rodents with Tumors | % |
|---|---|---|---|
| Control | 89 | 43 | 48 |
| Food Restricted | 77 | 0 | 0 |
| Control/Radiated | 102 | 91 | 89 |
| Restricted/Radiated | 128 | 29 | 23 |

From: Gross L, Dreyfuss Y. Prevention of spontaneous and radiation-induced tumors in rats by reduction of food intake. Proc Natl Acad Sci U S A. 1990 Sep;87(17):6795-7.B. YU. Aging and oxidative stress: modulation by dietary restriction. Free Radic Biol Med. 1996;21(5):651-68.

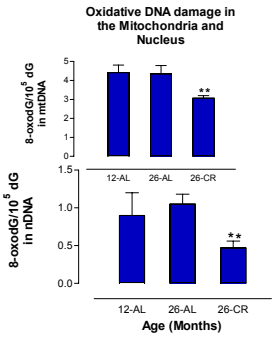
**Hot spots for free radical attack:**

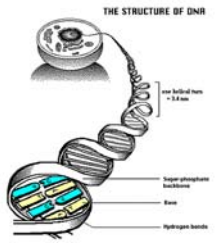


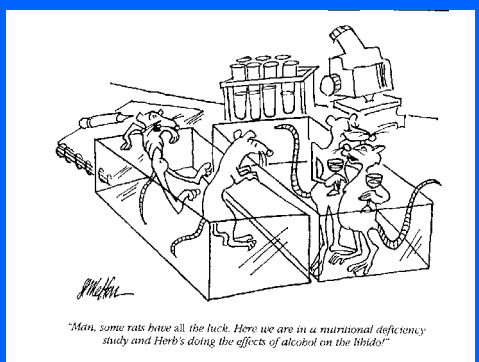




Drew, B., Phaneuf, S., Dirks, A., Selman, C., Gredilla, R., Lezza, A., Barja, G., and Leeuwenburgh, C. (2002) Effects of aging and caloric restriction on mitochondrial energy production in gastrocnemius muscle and heart. *Am J Physiol.*



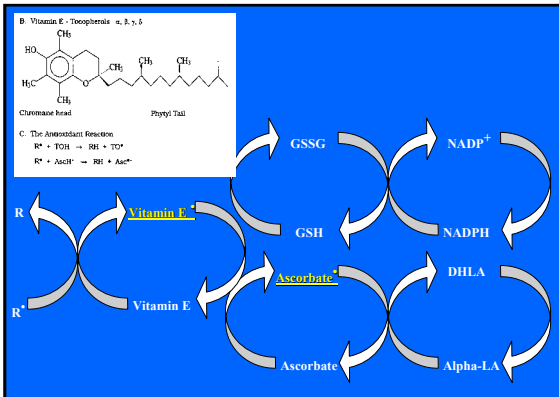
*"Man, some rats have all the luck. Here we are in a nutritional deficiency study and Herb's doing the effects of alcohol on the libido!"*

# Antioxidant Supplementation

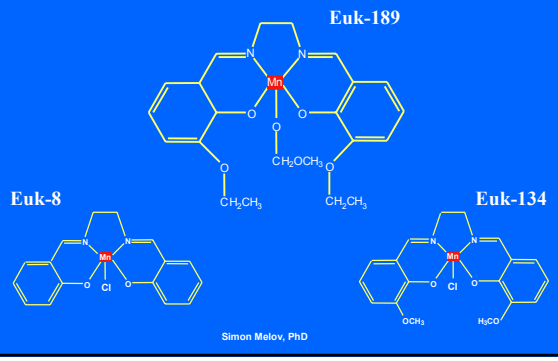
- Is there evidence that antioxidant supplementation prolongs **maximal** life-span?
- We would all like a pill to live longer……, but


The effect of antioxidant supplementation mean and maximum life-span

| SHORT-LIVED-SPECIES | (Mean) | (Max) | |
|---|---|---|---|
| Tocopherol-*p*-chloro-phenoxyacetate | (13.0) | (13.0) | *Drosophila* |
| *d*-Tocopherol | (31.4) | (23.2) | Nematodes |
| Vitamin E | (16.8) | (15.4) | Rotifer |
| Sulfhydryl agent | (28.0) | | Rotifer |
| N-acetylcysteine | (26.6) | | *Drosophila* |
| SOD – Mimetics | (30-40) | (30) | *C. Elegans* |
| **LONGER-LIVED-SPECIES** | | | |
| Mercaptoethylamine 0.05% | (12.8 ) | (0) | Mice |
| Mercaptoethylamine 1.00% | (29.2) | (0) | Mice |
| Santoquin (0.5%) | (18.1) | (0) | Mice |
| Vitamin E, Vitamin C, b-carotene | (0) | (0) | Rats |



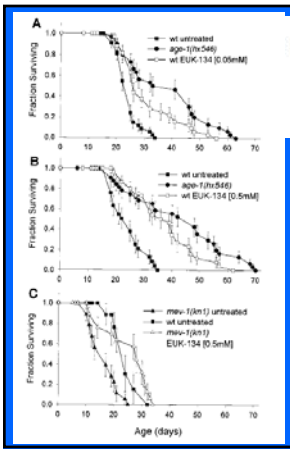

## Catalytic antioxidants tested in *Sod2-/-* mice, and in aging paradigms




Simon Melov, PhD

# What is a good Antioxidant?

- What is an antioxidant?
- A substance when present in trace (small) amounts inhibits the oxidation of the bulk
- What are considered good antioxidants ?
  - Relatively un-reactive (antioxidant•)
  - Repaired Rapidly
  - Decays to harmless products

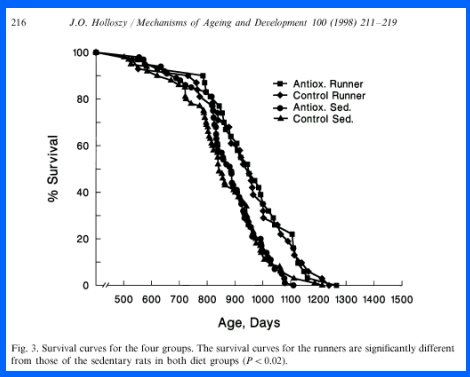



**Extension of Life-Span with Superoxide Dismutase/Catalase Mimetics**

Simon Melov,[1] Joanne Ravenscroft,[1]* Sarwatt Malik,[2] Matt S. Gill,[2] David W. Walker,[2]† Peter E. Clayton,[2] Douglas C. Wallace,[3] Bernard Malfroy,[4] Susan R. Doctrow,[4] Gordon J. Lithgow[2]‡

www.sciencemag.org SCIENCE VOL 289 1 SEPTEMBER 2000

- Mean lifespan increase of 45%
- Maximum lifespan was increased up-to 105%
- No dose dependence
- No differential between EUK-8 or EUK-134



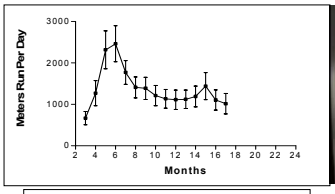

-Antioxidants have no effect on longevity

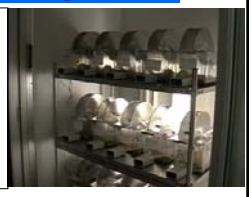
-Exercise increase mean life-span

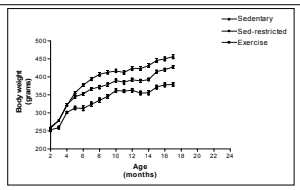
## To Increase Maximum Life-Span…

- A key may be to… reduce **ENDOGENOUS chronic oxidant production**
- A key may be to… reduce **ENDOGENOUS levels of specific cytokines**
- A key may be to… reduce **ENDOGENOUS accumulation of protein aggregates and glycooxidation products**
- Reduce **mitochondrial and nuclear DNA damage** and/or increase repair

**What are the cellular adaptations of LIFE LONG EXERCISE to explain increase in mean life-span?**



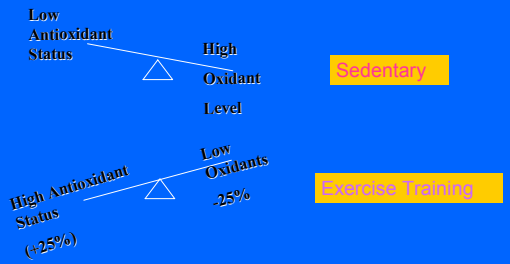



## Primary Interventions

Could Effect Primary Aging

- Life-style
  - 1) Diet (Caloric Restriction)
    - Avoid Restaurants (a treat now and then is ok)
    - Learn how to cook healthy yourself
    - Shop Smart
    - "Empty refrigerator" before going to the store
    - Some evenings -just have a salad
    - Food actually taste better when you caloric restrict
    - You will not be miserable…. life is short and you want to stay away from the doctor during the last 15-20 years of your life-span
    - Comes down to how much discipline you have
  - 2) Moderate exercise ?? (mean life span)
    - increase daily activities and enjoy your exercise or walking program
  - 3) Take your antioxidants ??? (maybe mean live span)
    - Eat a diet high in fruits, veggies, and herbs

## We will investigate mitochondrial efficiency and deletions as well as oxidant and antioxidant balance?




## Secondary Interventions

May be beneficial if you first follow primary interventions and these will also prevent secondary aging

- Wine (1 serving) and Dark Beer (1 serving)
- Aspirin (COX, **TNF-α / NF-κB** inhibitor)
- AGE-breakers (amino guanidine)?
- ACE-inhibitors; reduces inflammation in patients with heart disease.
- Hormone therapy; DHEA after ~60years?? Estrogen is out-in?, Testosterone…. when levels decline??

## Why these?

- Currently we don't need a **genetic miracle** to prolong healthy life. Stop **smoking**, perform **regular** exercise, effective **stress** management, **stay lean** and a provide yourself with a heart-healthy diet. This could increase your mean-life-span by:

**20 to 25 HEALTHY years beyond the age of 70**



## ACKNOWLEDGEMENTS

**Biochemistry of Aging Lab:**
Barry Drew, PhD (USA)
Amie Dirks, PhD (USA)
Sharon Phaneuf (USA)
Suma K. PhD (India)
Rajani Shelke, PhD (India)
Colin Selman, PhD (Scotland)
Tracey Philips, (Scotland)
Mina Hiona (Greece)
Young Yang (Korea)
Lori Armstrong (USA)

**Collaborators:**
Gustavo Barja, PhD (Spain)
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Steve Dodd, PhD (USA)
Scott Powers, PhD (USA)
Angela Lezza, PhD (Italy)
Nicola Gadaleta, PhD (Italy)
David Julian, PhD (USA)
Tilman Grune, PhD (Germany)

**Funding Provided by:**
National Institute of Health
National Institute on Aging
Society of Geriatric Cardiology