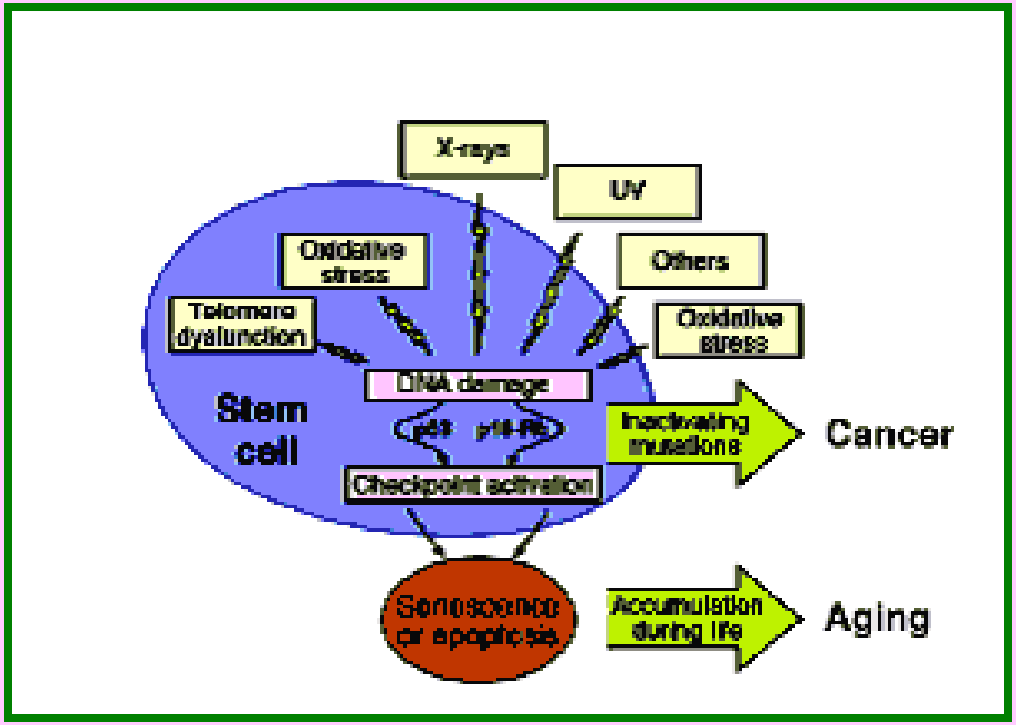
營養與老化 (00070115)

Nutrition and Aging

Mechanisms of Aging



保健營養學系三年級

授課教師：保健營養學系 趙振瑞(Jane Chao)教授

Tel: 2736-1661 ext.6548; E-mail: chenjui@tmu.edu.tw

Learning Objectives

- Theory of Aging
- Factors Influencing Aging Process
- Nutrient Intake and Aging

References

- **Geriatric Nutrition: The Health Professional's Handbook (2006, 3rd ed) Ronni Chernoff, Jones and Bartlett Publishers, Inc.**
- **Nutrition in Aging (1997, 3rd ed) Schlenker, ED. William C. Brown**

The Oldest People

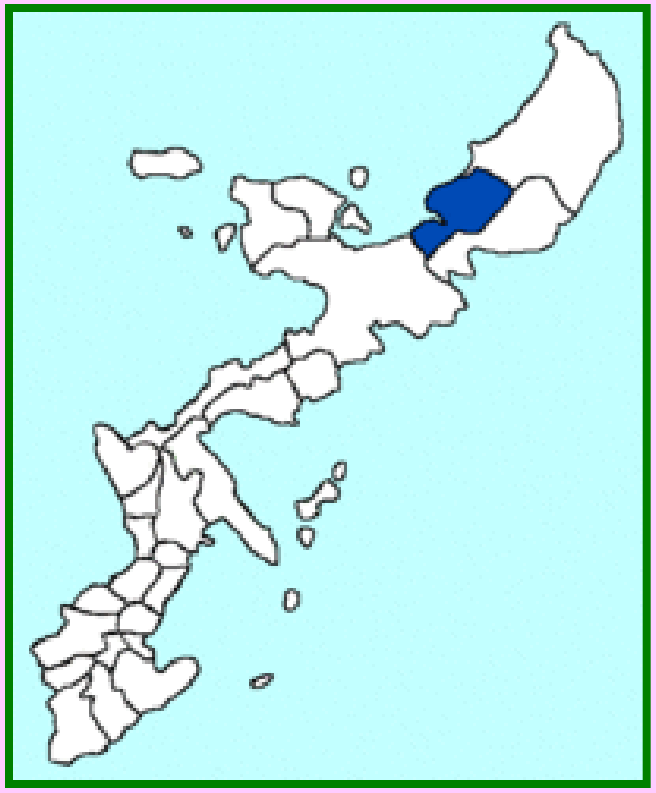
- *Supercentenarian: ≥ 110 yr*
- *Jeanne Calment (F) of France (1875 ~ 1997), was aged 122 years and 164 days*
- *Shigechiyo Izumi (M) of Japan (1865 ?~1986) was aged 120 years and 237 days*
- *Sarah DeRemer Knauss (F) of USA (09.24.1880~12.30.1999), was aged 119 years and 97 days*
- *Lucy Hannah (F) of USA (07.16.1875 ~ 03.21.1993) is aged 117 yr and 248 days*
- *among top 10 oldest (113~114 yr) people currently living: 9 are females, 6 live in USA, 2 live in Japan, 1 lives in UK or France*

Kama Chinen from Okinawa, Japan @ 114 y

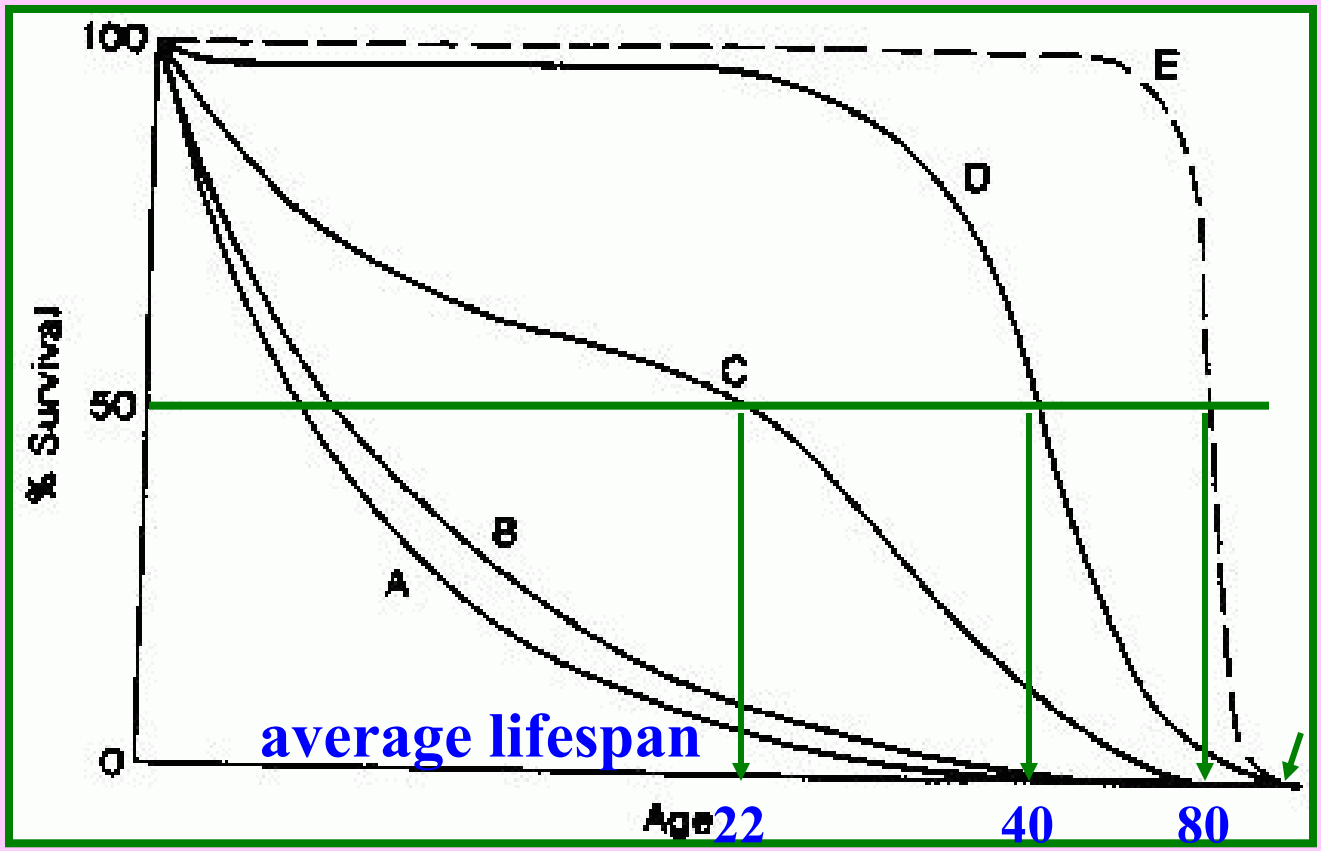
http://www.deaflion.com/wp-content/uploads/2009/09/Kama-Chinen1.jpg

日本長壽村

- 日本琉球列島沖繩島大宜味村 (おおぎみそん)
- 90歲以上者46人，佔總人口的1.3%



http://upload.wikimedia.org/wikipedia/commons/thumb/0/02/Ogimi_in_Okinawa_Map.gif/200px-Ogimi_in_Okinawa_Map.gif



A: exponential decay (指數衰減) curve

B: to the survival of small animals, such as mice or squirrels

C: human survival curve when average lifespan was 22 yr

D: human survival curve when average lifespan was 40 yr

E: human survival curve when average lifespan was 80 yr

http://www.benbest.com/lifeext/aging.html

Theory of Aging

- **Hayflick (1977) tissue cultures (most cellular systems) are able to undergo only 40~50 doublings (no. of cell division)**

  → finite life span no immortal

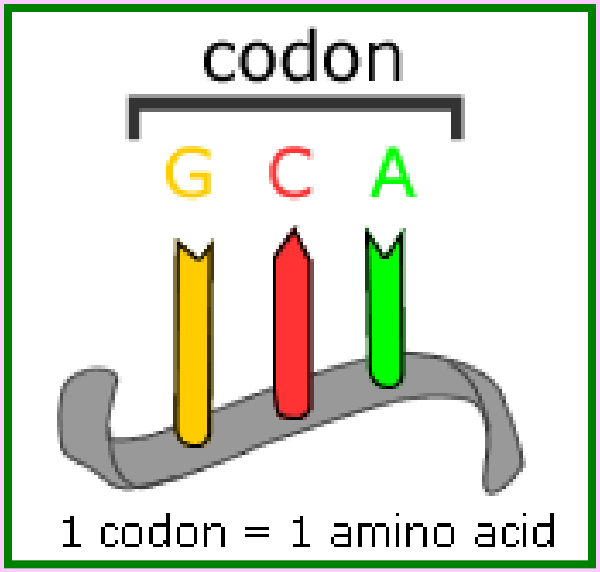
- **biological theory:**
  - **genetic: damage to DNA or errors in transmission of information**
  - **nongenetic: chemical or structural changes induced by environmental factors**

Genetic Theory of Aging

- human with long-lived parents and grandparents live ~ 6 yr longer than those with parents and grandparents who died < 50 yr
- a genetic program sets upper limits of life span in a species
- familial characteristics influence differences in life span
- genetic programs can be altered by environmental factors

Genetic Theory of Aging

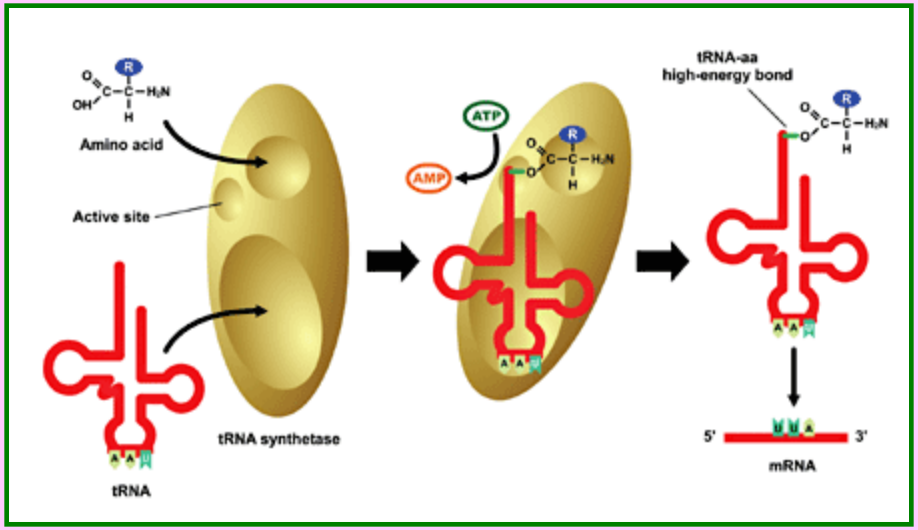
- DNA readout - codon restriction
- DNA damage - somatic mutation
- error theory
- telomere theory
- Hayflick limit theory



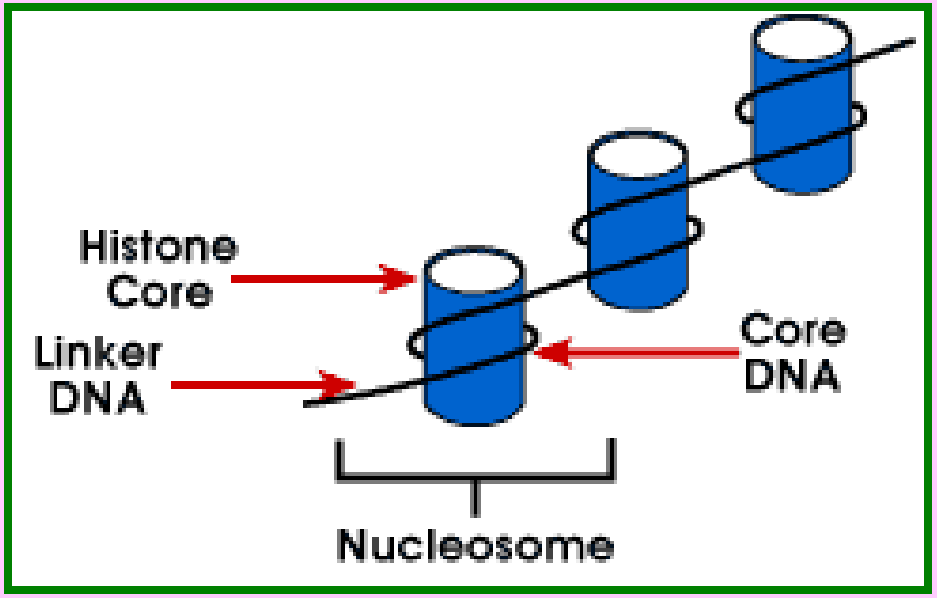
http://www.bio.georgiasouthern.edu/

DNA Readout – Codon Restriction

- aging is accompanied by changes in the types of aminoacyl-tRNA synthetases present in cells
- histones are more tightly bound to chromatin than in young



http://journals.prous.com/journals/dnp/20061906/html/dn190347/images/fig1.gif



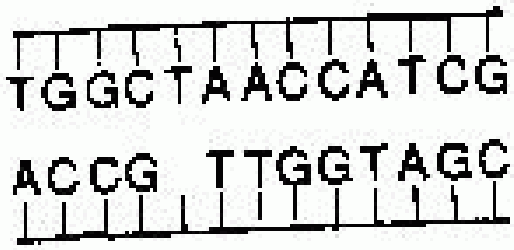
http://www.ndsu.edu/pubweb/~mcclean/plsc431/eukarychrom/histone.gif

DNA Damage – Somatic mutation

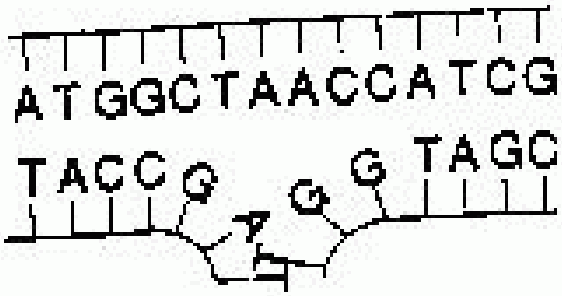
- slight differences in the structure of protein formed

TYPE OF DAMAGE	events/cell/d	% of total daily damage
Single-strand break	120,000	50.9
N^7-Methylguanine	84,000	35.6
Depurination	24,000	10.2
O^6-Methylguanine	3,120	1.3
Oxidized DNA	2,880	1.2
Depyrimidation	1,320	0.5
Cytosine deamination	360	0.2
Double-strand breaks	9	0.01
Interstrand cross-links	8	0.01

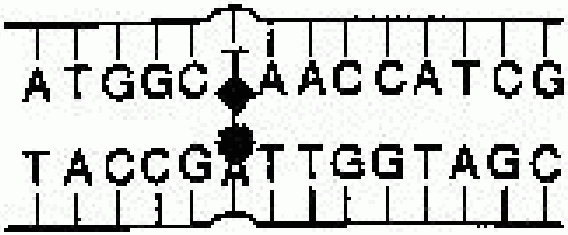
http://www.benbest.com/lifeext/aging.html



DEPURINATION



SINGLE-STRAND BREAK



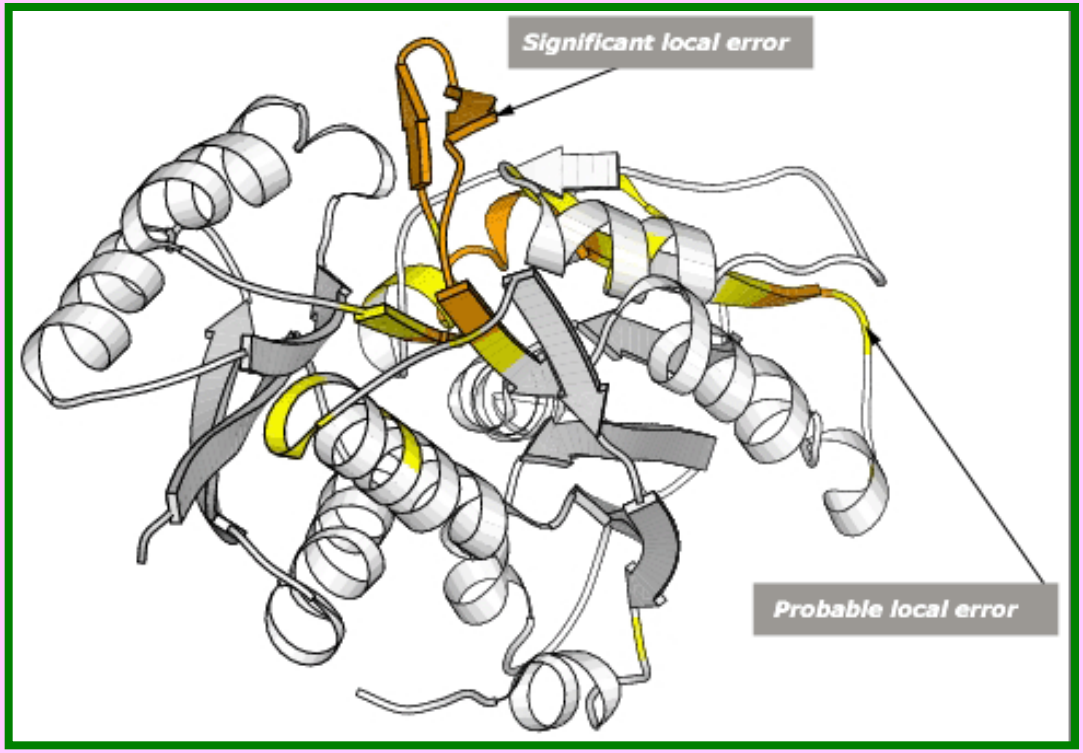
CROSS-LINK

http://www.benbest.com/lifeext/aging.html

Error Theory

- the production of proteins and the reproduction of DNA sometimes is not carried out with accuracy

- the accumulation of these flawed molecules can cause diseases and other age changes to occur



Telomere Theory

- at the ends of each chromosome is a long non-functional strand of DNA
- consist of the 6-base repeating sequence 5'-TTAGGG-3'
- at conception each human telomere is about 10 k bp long (ie, about 1,666 TTAGGG repeats)
- the typical chromosome is about 13,000 times longer (130 million bp)
- telomeres lose an average of 8 TTAGGG subunits per cell division
- at birth (9 mo. later), the average telomere is half as long as it was at conception

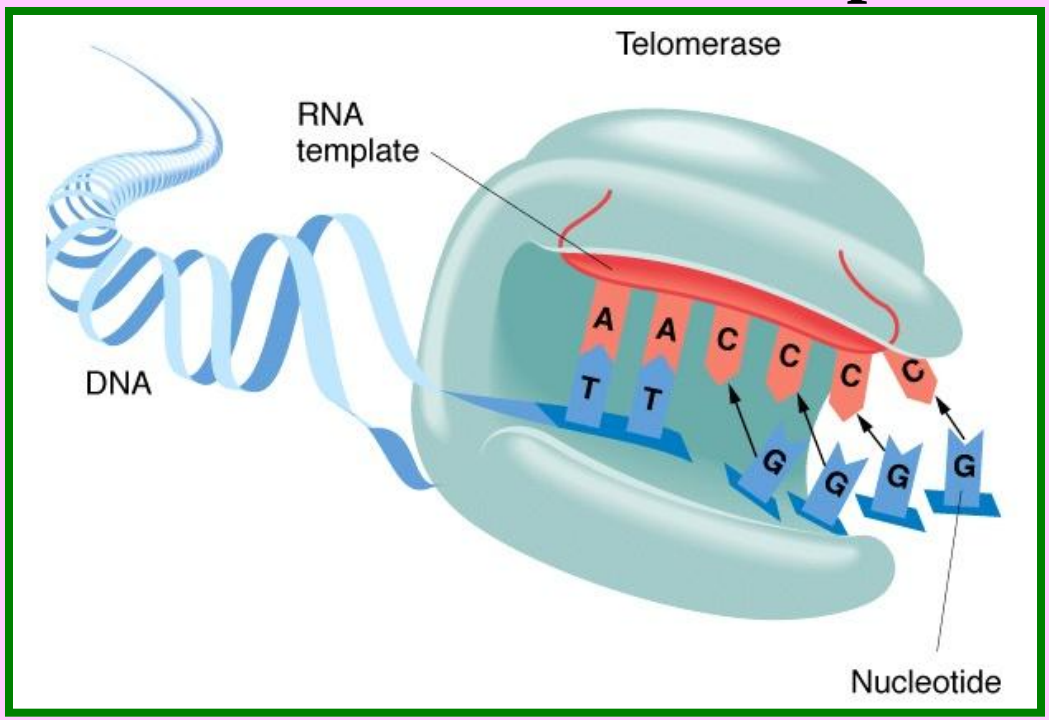
Telomere Theory

- with each cell division, some of the telomere is lost because DNA polymerase cannot complete the 5‘-end and therefore leaves a single-strand 3’-end overhang
- the number of times that most dividing cells can divide is limited by telomere length
- telomeres shorten more rapidly in short-lived mammals & birds than in long-lived ones
- germ cells (sperm or egg), stem cells (undifferentiated cells) and "immortalized" cancer cells contain telomerase that replaces lost telomeres

Telomere Theory

- **telomerase is a reverse transcriptase, making DNA from an RNA template**

- **in adults, telomerase is expressed in cells that need to divide regularly (e.g., in the immune system), although most somatic cells do not express it**



http://www.uic.edu/classes/bios/bios100/f05pm/telomerase.jpg

Hayflick Limit Theory

- **human cells are limited in the number of times it can divide, which can be affected by waste accumulation**

- **human cells ability to divide is limited to approximately 50-times, after which they simply stop dividing (and hence die)**

Nongenetic Theory of Aging

- wear and tear theory
- deprivation theory
- waste accumulation (membrane) theory
- cross-linking (glycosylation) theory
- free radical theory
- mitochondrial decline theory
- neuroendocrine theory

Wear and Tear Theory

- the body and its cells were damaged by overuse and abuse

- the cells and organs are worn down by toxins in our diet and in the environment; by the excessive consumption of fat, sugar, caffeine, alcohol and nicotine; by the ultra-violet rays of the sun and by the many other physical and emotional stresses to which we subject our bodies

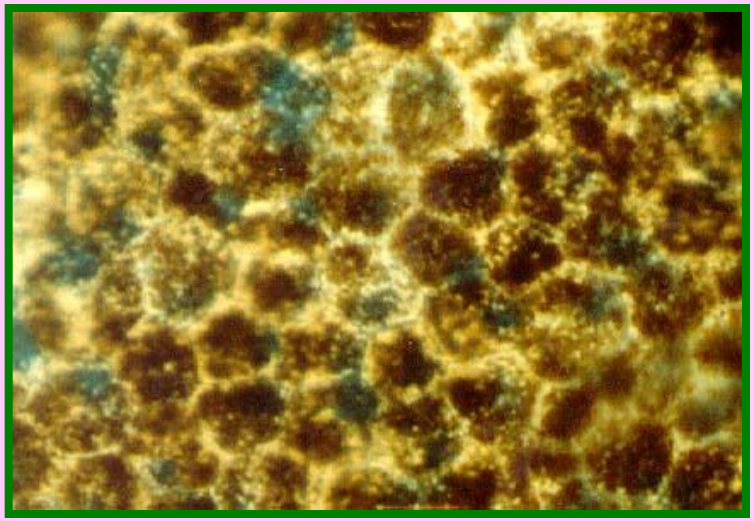
Deprivation Theory

- **inadequate delivery of essential nutrients or O_2**

http://www.elanso.com/U/A/20080320/63341577640 2072500/12850454402072500.jpg

Waste Accumulation Theory

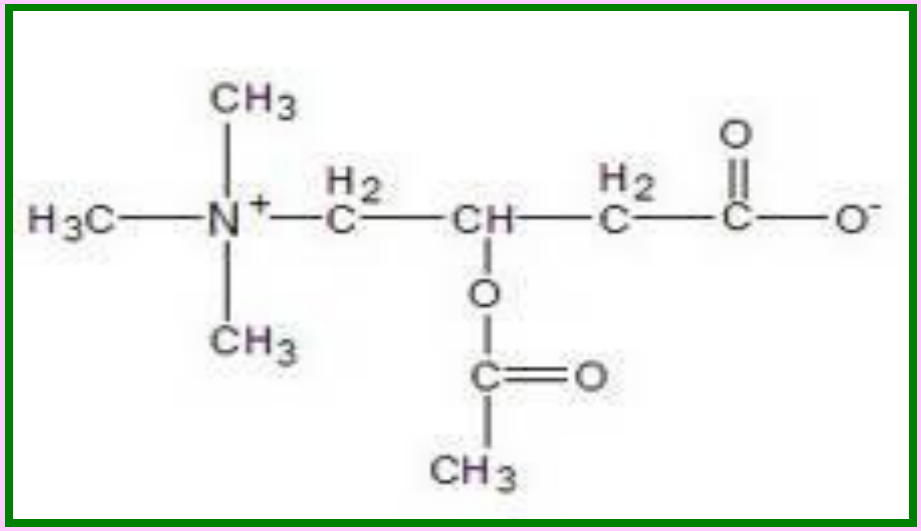
- accumulation of deleterious substances
- lipofuscin (脂褐素) is formed by a complex reaction that binds fat in the cells to proteins
- lipofuscin is common in the neurons, muscle fibers of heart, lungs, skin, adrenal cortex, and testicle



http://starklab.slu.edu/lipofuscin.JPG

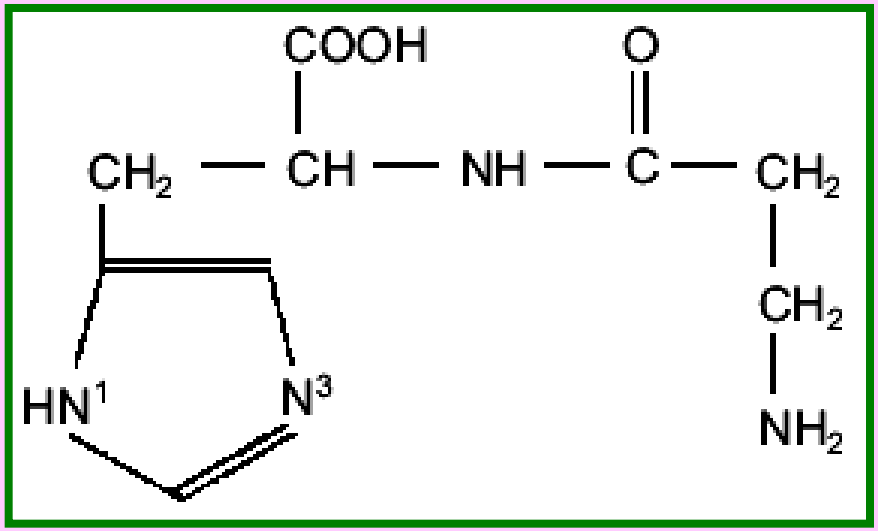
Waste Accumulation Theory

- **acetyl-L-carnitine (ALC) and carnosine (β-alanyl-L-histidine) help to chelate ionic metals (flush toxins from the body) and to remove lipofuscin**



acetyl-L-carnitine

http://www.scientificformulations.com/components/Acetyl_L_Carnitine/acetyl_L_Carnitine1_clip_image002.jpg



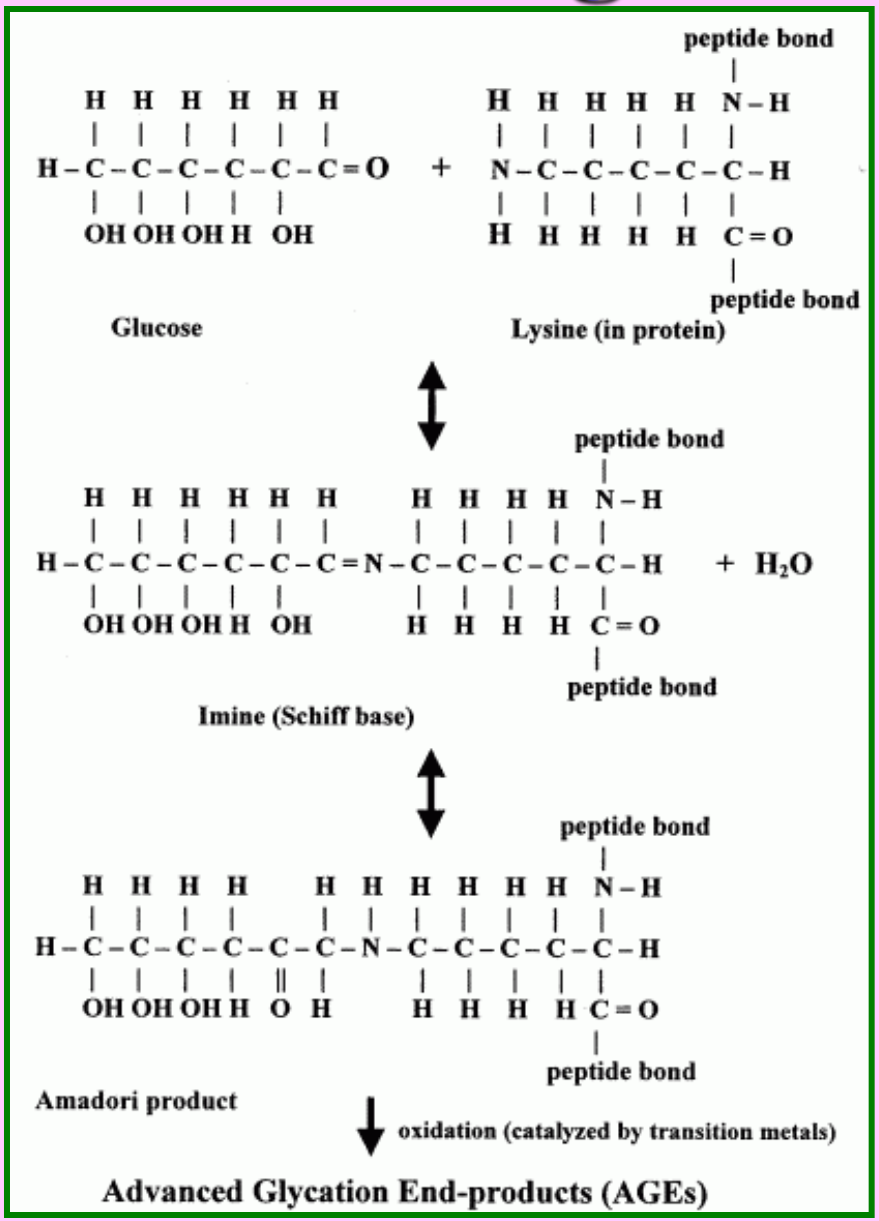
carnosine

http://www.1stvitality.co.uk/artwork/artwork/carnosine/carnosine_formula.gif

Cross-Linking Theory

- the binding of glucose (simple sugars) to protein: Maillard reaction, or non-enzymatic glycosylation, a process that occurs under the presence of oxygen → causes various problems
- binding to DNA may cause damage that leads to malformed cells and thus cancer
- responsible for cataract, cardiac enlargement, the hardening of collagen, and renal disorder
- diabetics have 2-3 times the numbers of cross-linked proteins when compared to their healthy counterparts

Cross-Linking Theory



http://www.benbest.com/lifeext/aging.html

Free Radical Theory

- **free radicals are known to attack the structure of cell membranes, which then create metabolic waste products**

- **toxic accumulations interfere with cell communication, disturb DNA, RNA and protein synthesis, lower energy levels and generally impede vital chemical processes**

- **most toxic: hydroxyl ($^{\bullet}OH$)-radical and superoxide ($O_2^{\bullet -}$) –radical**

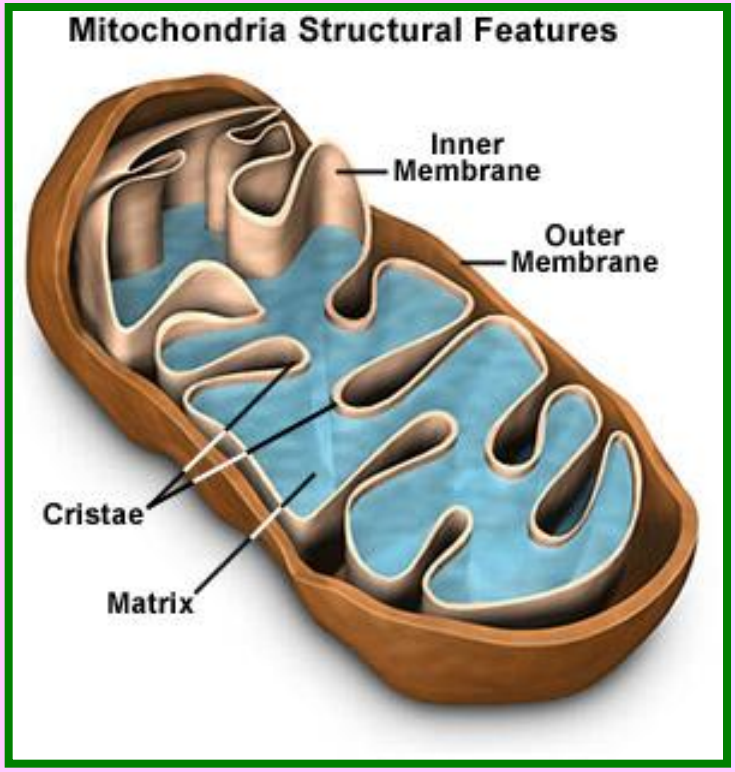
Table 3 Chemical Notation for various ROS/RNS

Radicals and Related Species	Name
$^1O_2$	singlet oxygen
$H^\bullet$	hydrogen atom
H^+	proton, hydron
$HO^\bullet$	hydroxyl radical
OH^-	hydroxide anion
H_2O_2	hydrogen peroxide
$RO^\bullet$	alkoxyl radical
$ROO^\bullet$	alkyldioxyl, alkylperoxyl radical
ROOH	alkyl hydroperoxide
$GS^\bullet$	glutathiyl radical
$^\bullet CH_3$	methyl radical
$^\bullet NO$	nitrogen monoxide, nitric oxide
$^\bullet NO_2$	nitrogen dioxide
N_2O	nitrous oxide
NO_2^-	nitrite
HNO_2	nitrous acid
NO_3^-	nitrate
HNO_3	nitric acid

http://www.water-air.com/image/water/Table3.jpg

Mitochondrial Decline Theory

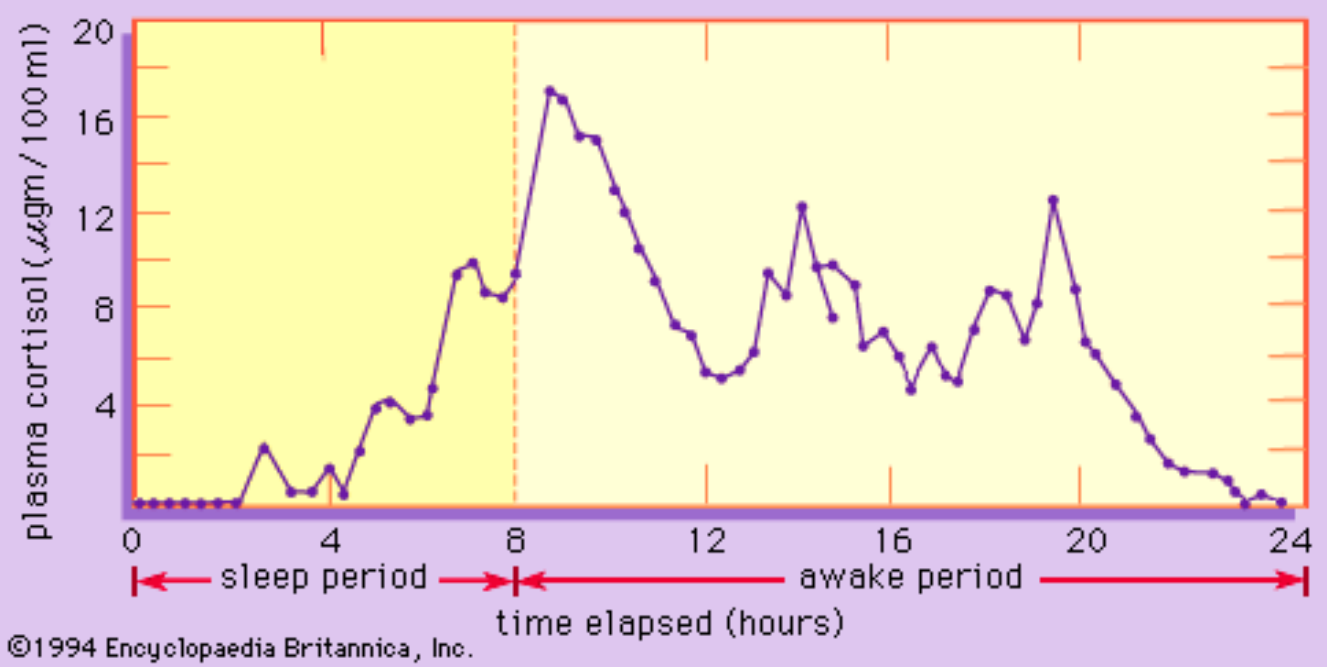
- **mitochondria become less efficient, fewer in number and larger**
- **ATP production declines**



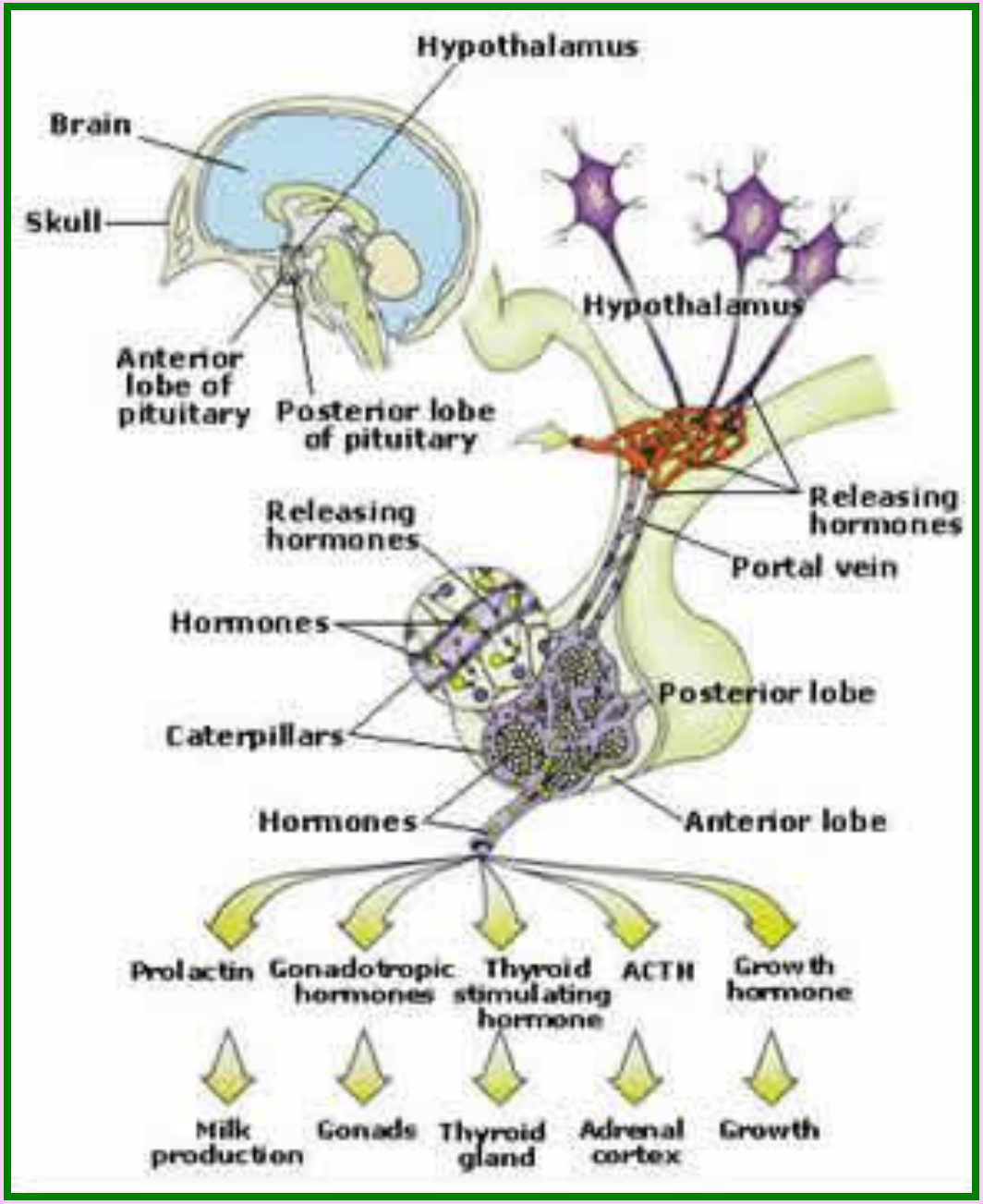
http://www.cartage.org.lb/en/themes/sciences/zoology/animalphysiology/anatomy/animalcellstructure/Mitochondria/mitochondria.jpg

Neuroendocrine Theory

- **the hypothalamus loss of regulation**
- **hypothalamus is damaged by the hormone cortisol**
- **cortisol is produced from the adrenal glands and considered to be a hormone responsible for stress**



http://media.web.britannica.com/eb-media/43/343-003-AB8288F3.gif



http://www.creationofman.net/chapter3/res/21.jpg

Factors Influencing Aging Process

- **intrinsic factors**

  genetic characteristics

  centenarians (≥ 100 yr-old people) produce more lymphocytes

  high specific activity of superoxide dismutase shows a longer life span

- **extrinsic factors**

  environmental factors

  nutrient intake

Nutrient Intake and Aging

- **Tokyo Metropolitan Institute of Gerontology (1988): the only factors effective in preventing aging are nutrition, exercise, and blood pressure control**

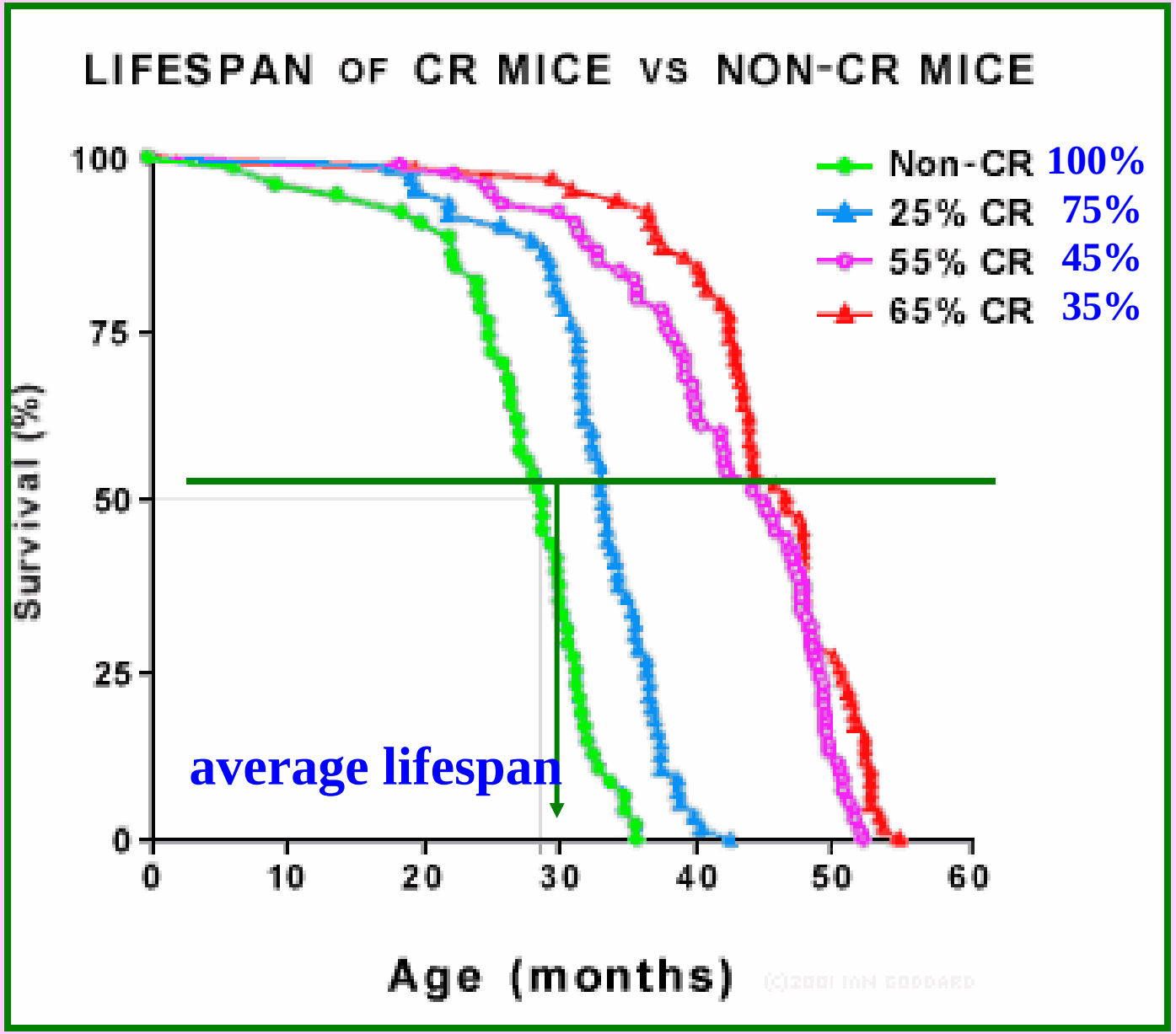
- **Eat to live and not live to eat –Franklin**

- **autointoxication—Metchnikoff (a Russian physiologist)**

death occurred as a result of toxins produced in a large intestine by fecal waste and then absorbed into the body

Nutrient Intake and Aging

- yogurt and other fermented milk products containing lactic acid-producing bacilli — destroy the intestinal microbes responsible for the poisonous waste
- caloric restriction ↑ life span
- below 50 percent takes you into actual calorie starvation, and the death rate increases

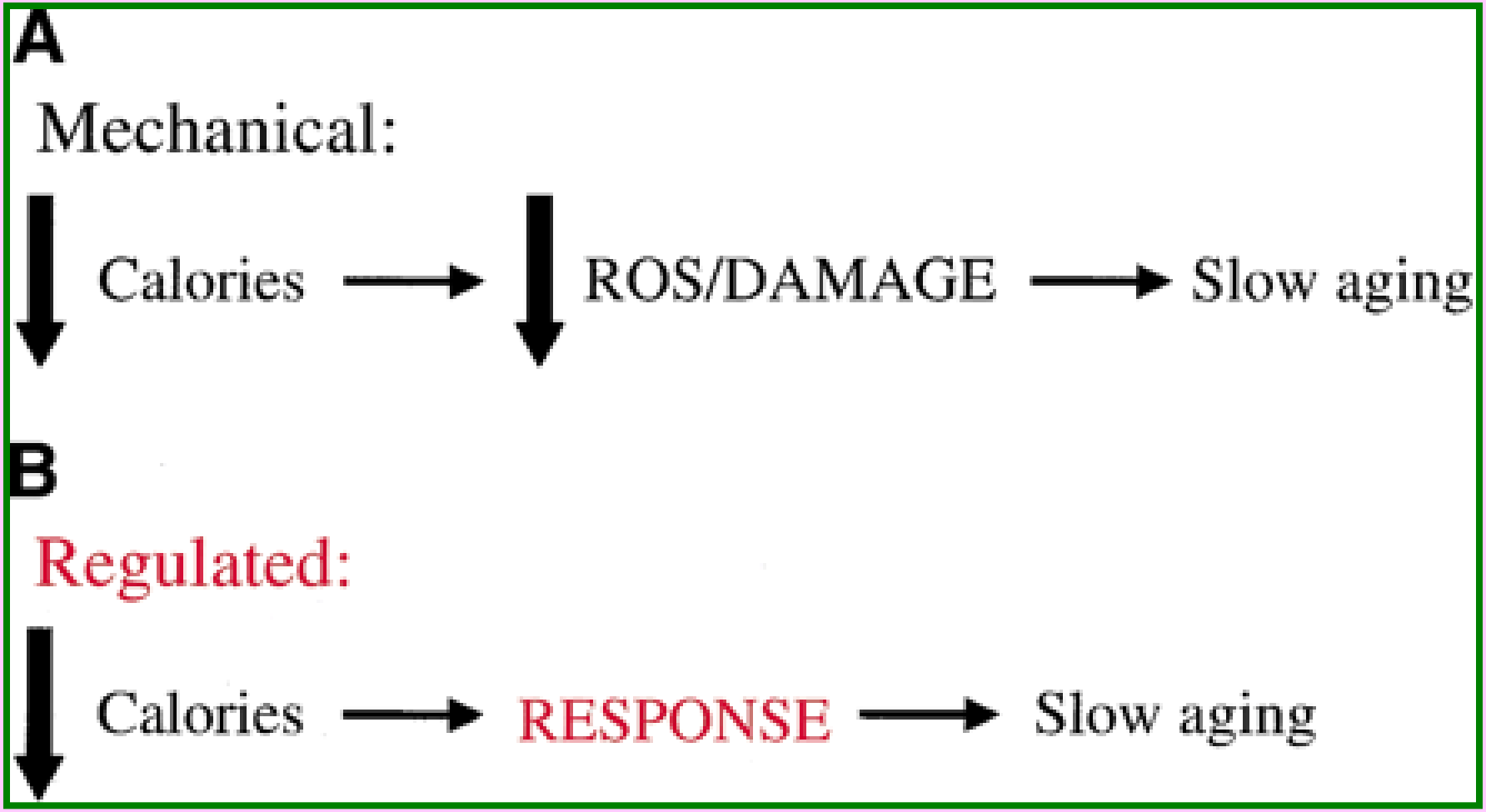


http://www.calorierestriction.org/

Caloric Restriction

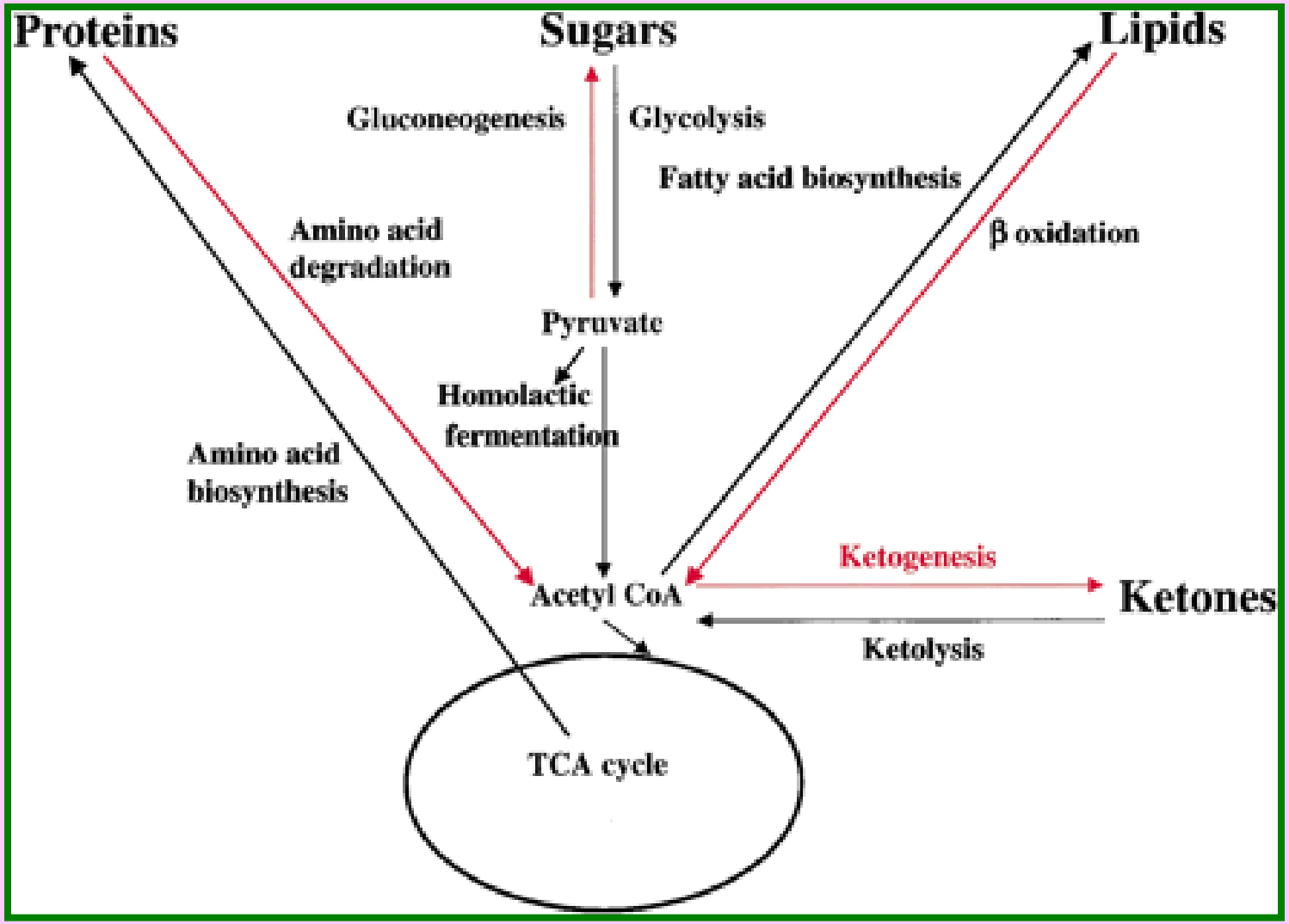
- ↑ DNA repair
- ↓ oxidative damage
- ↑ body's own antioxidant defense systems
  - ↑ heat shock protein (Hsp) response
- ↓ glycosylation
- delays age-related immunological decline
- most likely not going to die from a heart attack, stroke or diabetes

Caloric Restriction



Koubova and Guarente 2003

Caloric Restriction



up-regulation

down-regulation or no change

Koubova and Guarente 2003

http://www.cartoonstock.com/lowres/dco0071l.jpg

"I can assure you, this is the finest anti-aging formula money can buy. And I should know because I've been selling it for over 150 years."

Summary

- **Theory of Aging**
  - **Genetic**
  - **Nongenetic**
- **Factors Influencing Aging Process**
  - **Intrinsic factors**
  - **Extrinsic factors**