The Biology of Aging Revisited (S 1040)

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The first entry under "Presentations" is The Biology of Aging Revisited. Click on it and it will come up in a modified Power Point that you can go through by scrolling.

What is aging?

- Wine and people both mature and age
  - Both wine and people undergo structural and chemical changes after maturation.

(Do we improve with age, like wine?)

- Aging, as we will use the term, is defined as post maturational modifications in the structure, function and behaviors of living organisms.

Modes (types) of Aging

Chronological

Biological*

Psychological*

*heterogeneous (unlike, variable)
no two people age the same

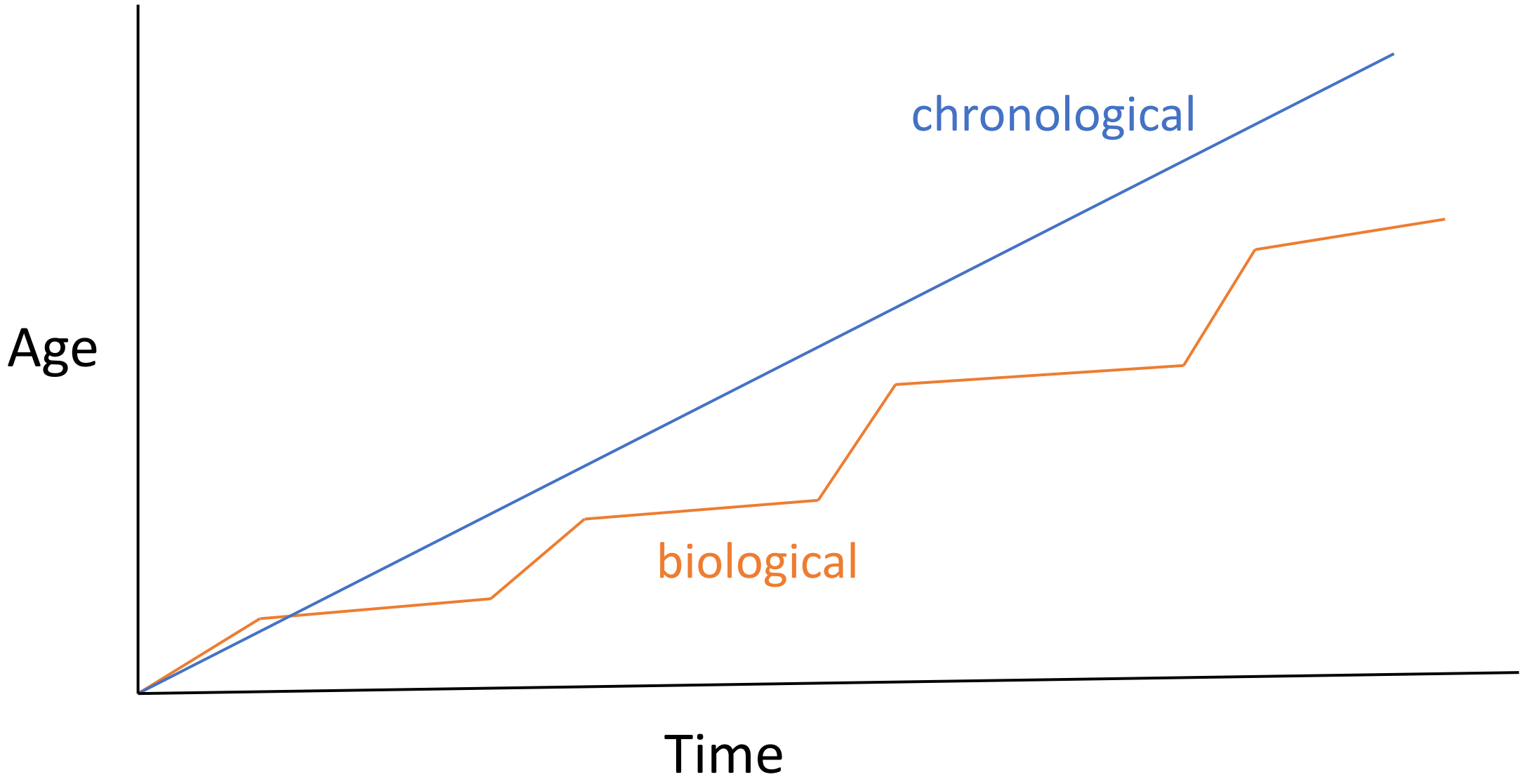
Heterogeneity of age:

Chronological age ≠ biological age ≠ psychological age

- Chronological age (homogeneous)
  (fixed, linear relationship between time and age)

  Biological age (heterogeneous)
  (variable, non-linear relationship between time and age)

  Psychological age (heterogeneous)
  (highly variable, little relationship between time and age)


chronological
biological
Age
Time

Twins with same biological age

Twins with different biological age

97 year old twins of different biological age

www.biological-age.com

Psychological age includes one's attitude toward aging

"*I started feeling old when I finished grad school at age 26.*"

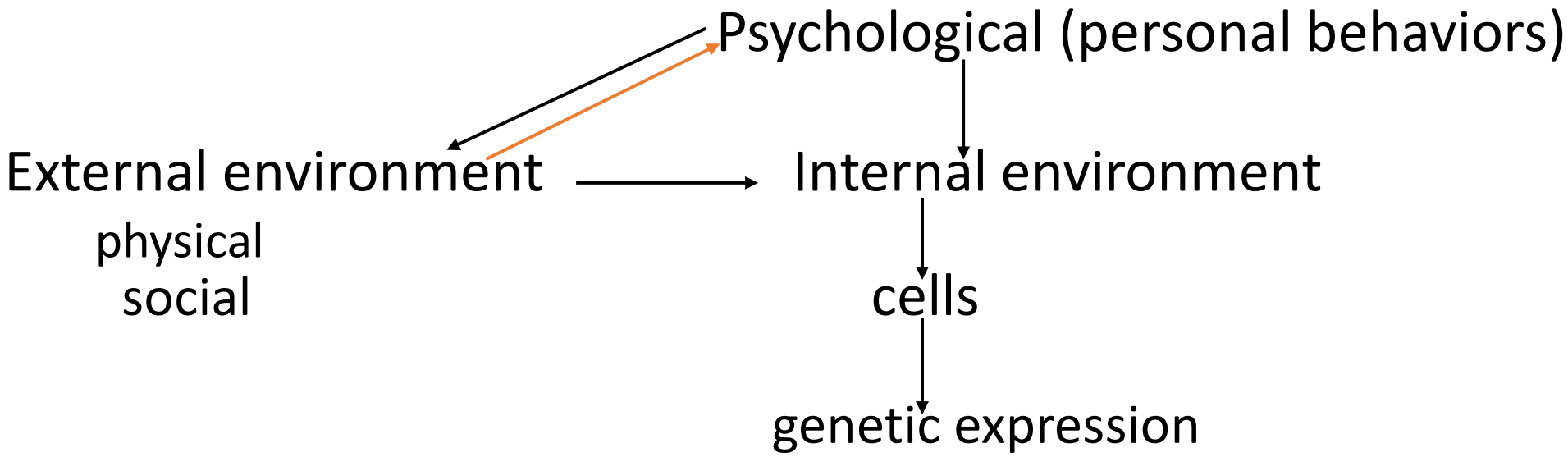
Henry, a college professor at about age 60

"*I guess that when I get old I'll have to get me one of those three wheeled* (motor) *bikes.*"

George, an avid motorcycle rider at age 87

What accounts for the heterogeneity of aging?

- Our day to day environment, both physical and social, has a strong influence on the body by way of the expression of genes.



The collective steps between activation of a gene and the resultant manufacture of a protein.

Questions?

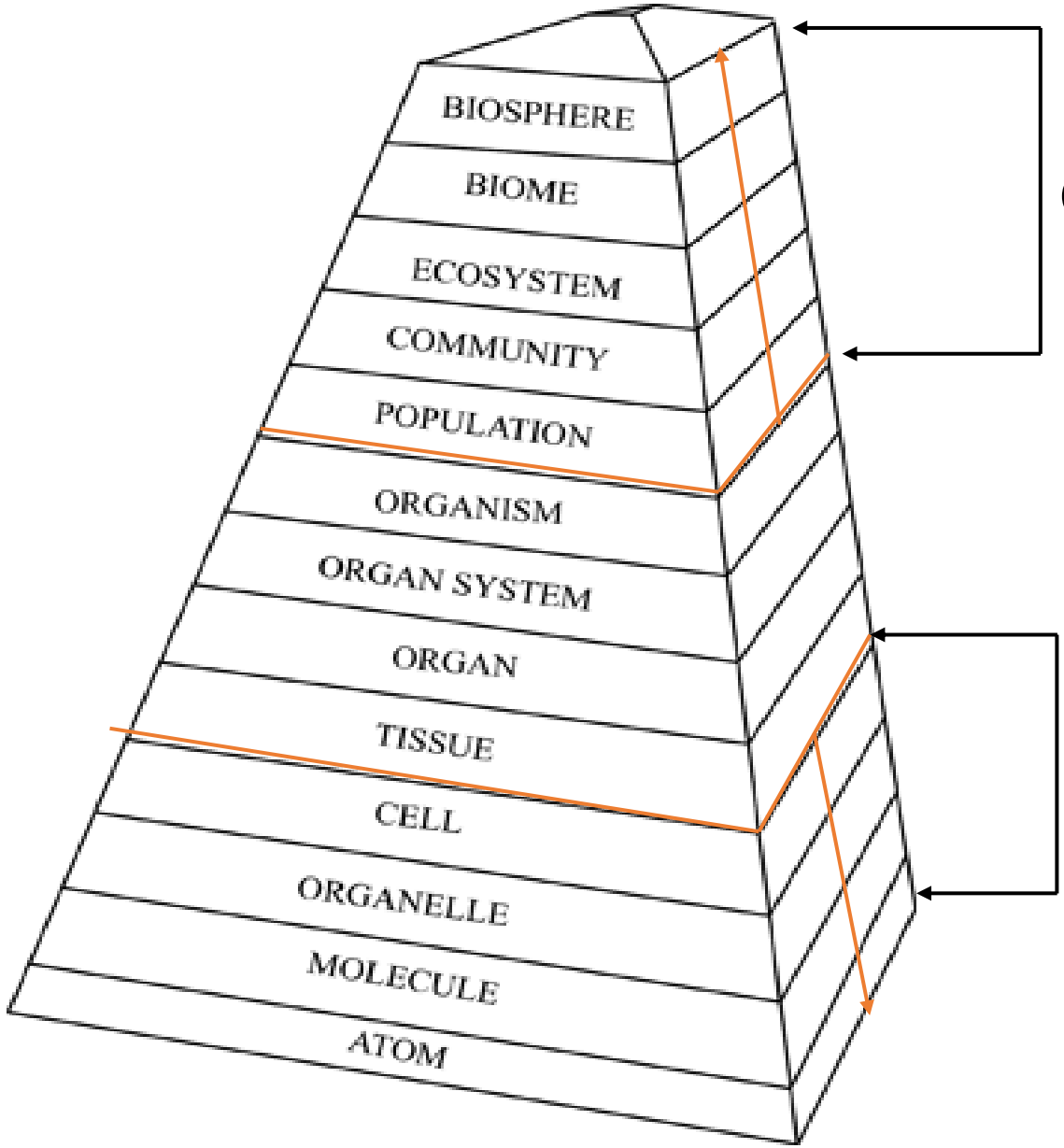
Top Down and Bottom up Theories* of Biological Aging

Global theories: Top down

Cellular theories: Bottom up

*Theories are statements of *testable* ideas for which their may or may not be existing data.

Hierarchy of living systems



Global theories (top down)

Cell theories (bottom up)

All living entities (e.g., the hierarchy of living systems) operate in an integrated and interdependent manner as a universal whole.*

**The Tao of Physics*, Fritjof Capra, Professor Theoretical Physics, Univ. Paris

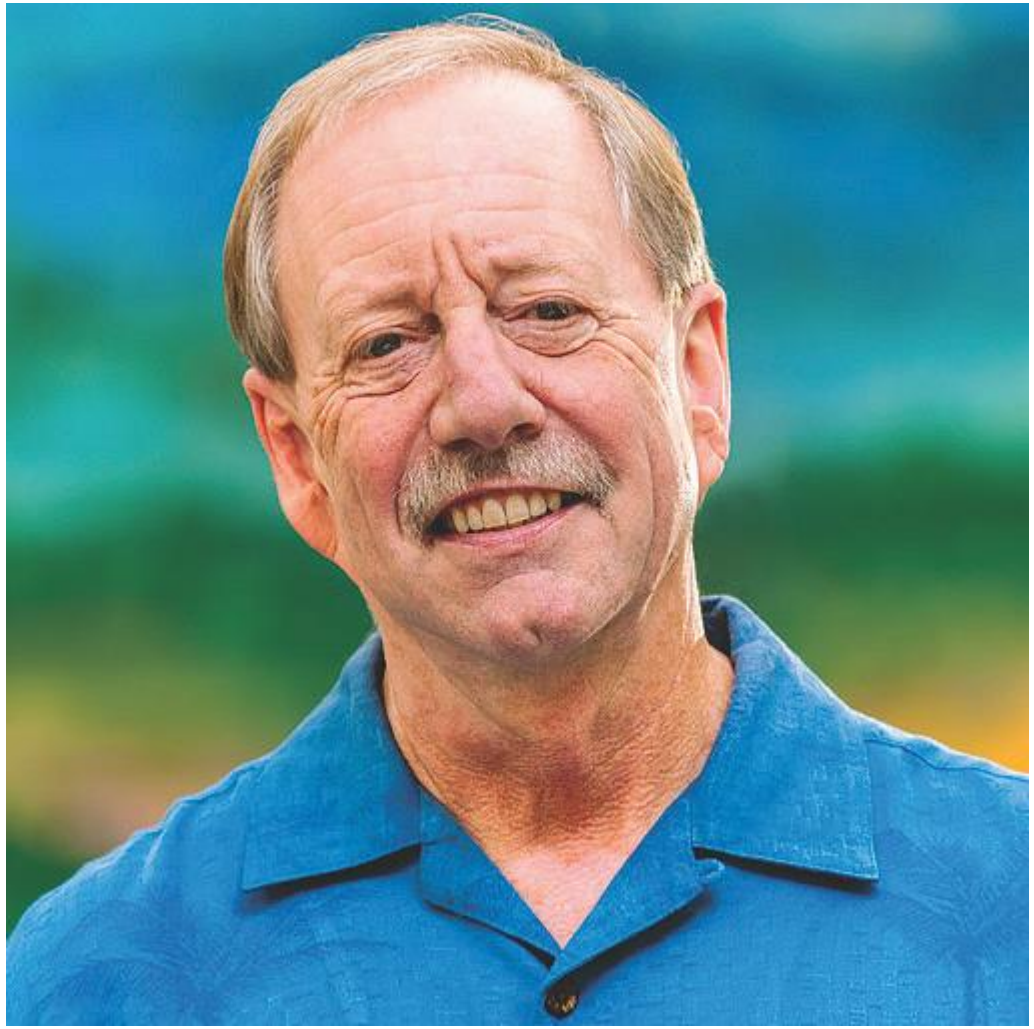
Environmental Influence on Aging (a global theory)

Rate of aging driven by the environment in which organisms live.

The more stressful the environment, the more rapid the rate of aging.

Steve Austad, Professor of Biology, Univ. Alabama

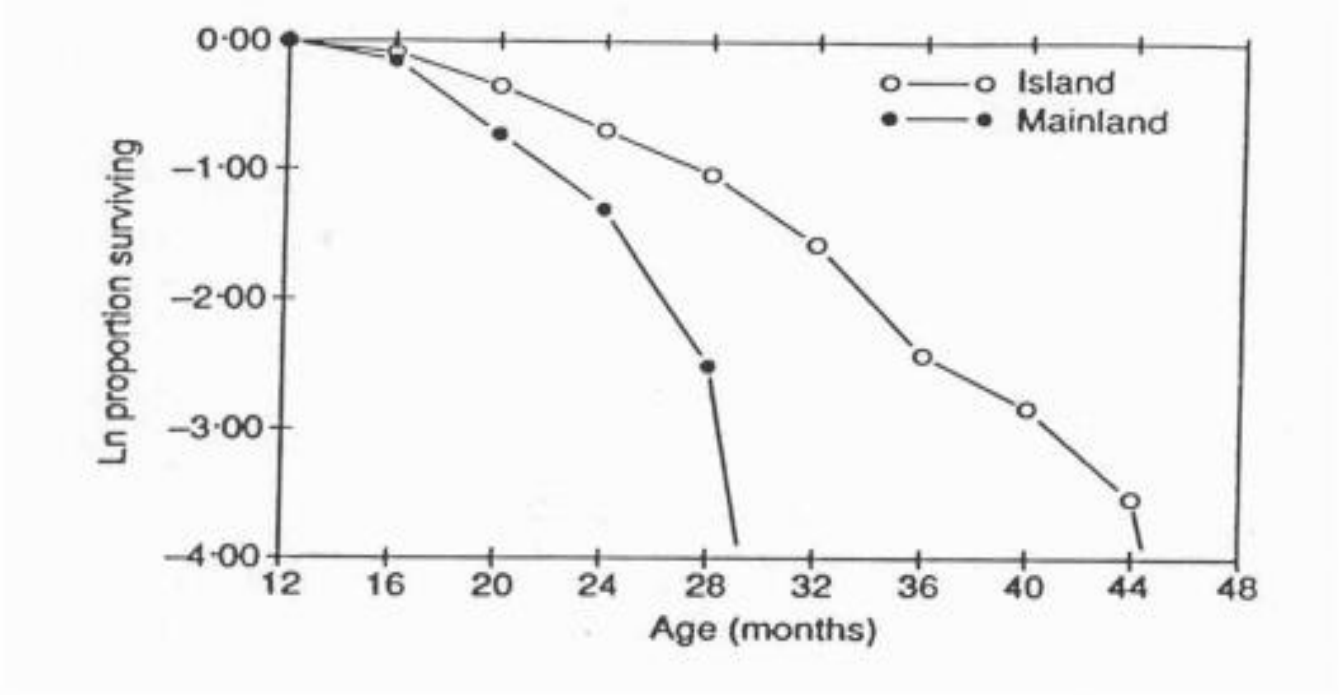
Sapelo Island opossum project: A test of the global theory of aging



Opossums who have evolved over multiple generations in the hazard free environment of Sapelo island were compared with opossums who have evolved in the hazard rich environment of mainland Georgia.

Survival rates* of mainland vs island opossums

(Steven N. Austad "*Why We Age*" Wiley & Sons Pub., 1997)



Island, hazard free environment

Mainland, hazard rich environment

*A reduced survival rate could be due to hazards alone or hazard induced aging.

Ln = natural logarithm

Indicators of aging in mainland vs island opossums (Austad, 1997)

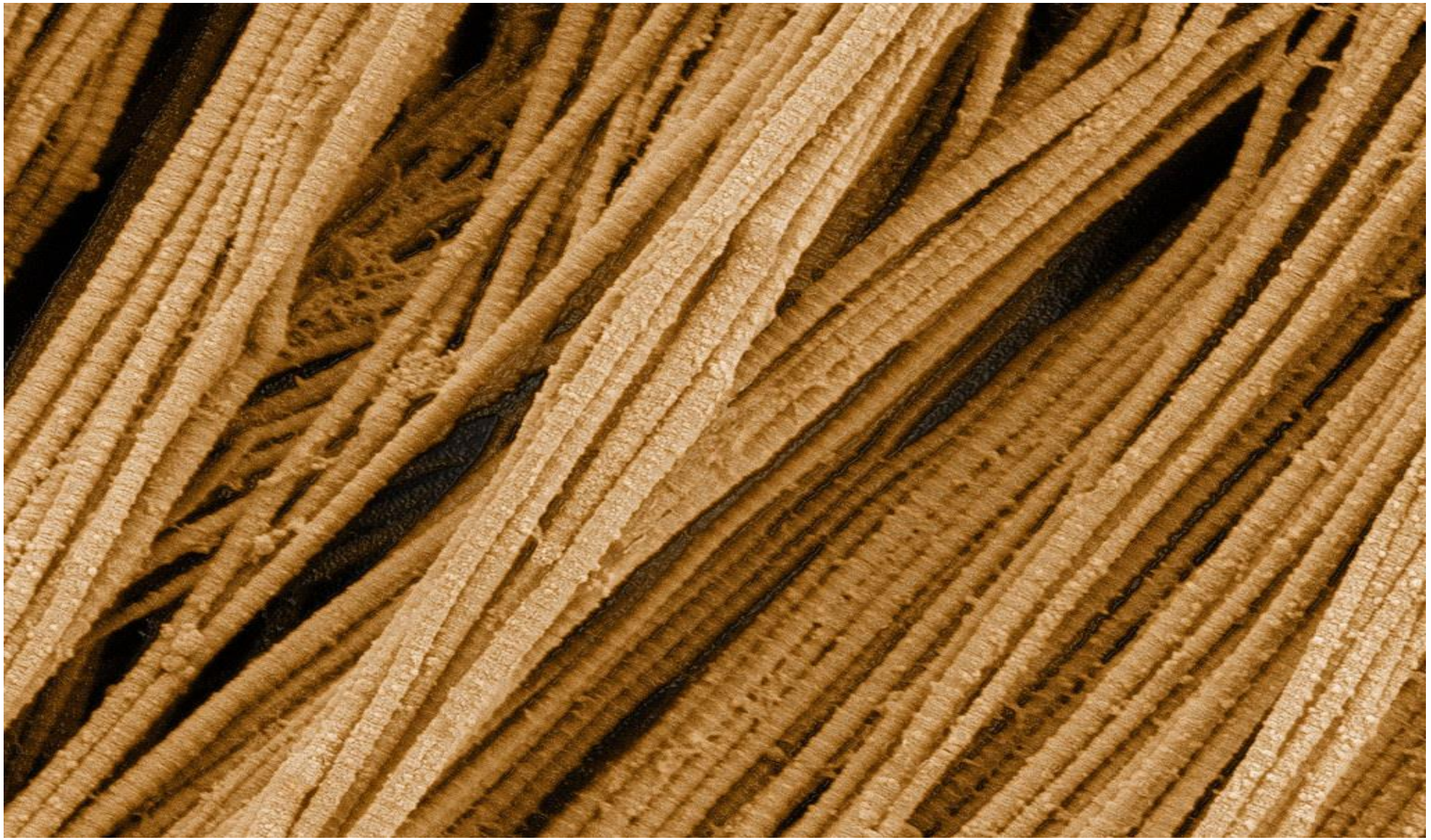
- Higher reproductive rate in mainland animals (6 pups vs 4 pups per liter)

more genetic energy going into survival of the specie
(the central objective of evolution according to Darwin)

results in a more rapid rate of reproductive system aging

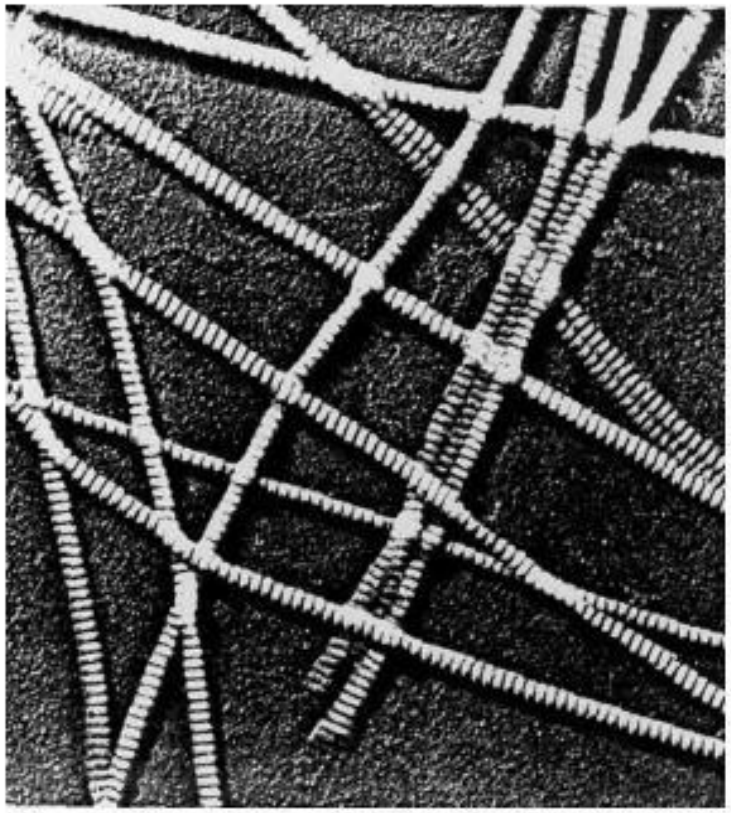
- More rapid aging of tissues as exemplified in stiffer tendons

Electron micrograph of collagen fibers, main component of tendons



Collagen Fibers

Young



Aged

Apparatus for measuring tensile strength (breaking point) of a material

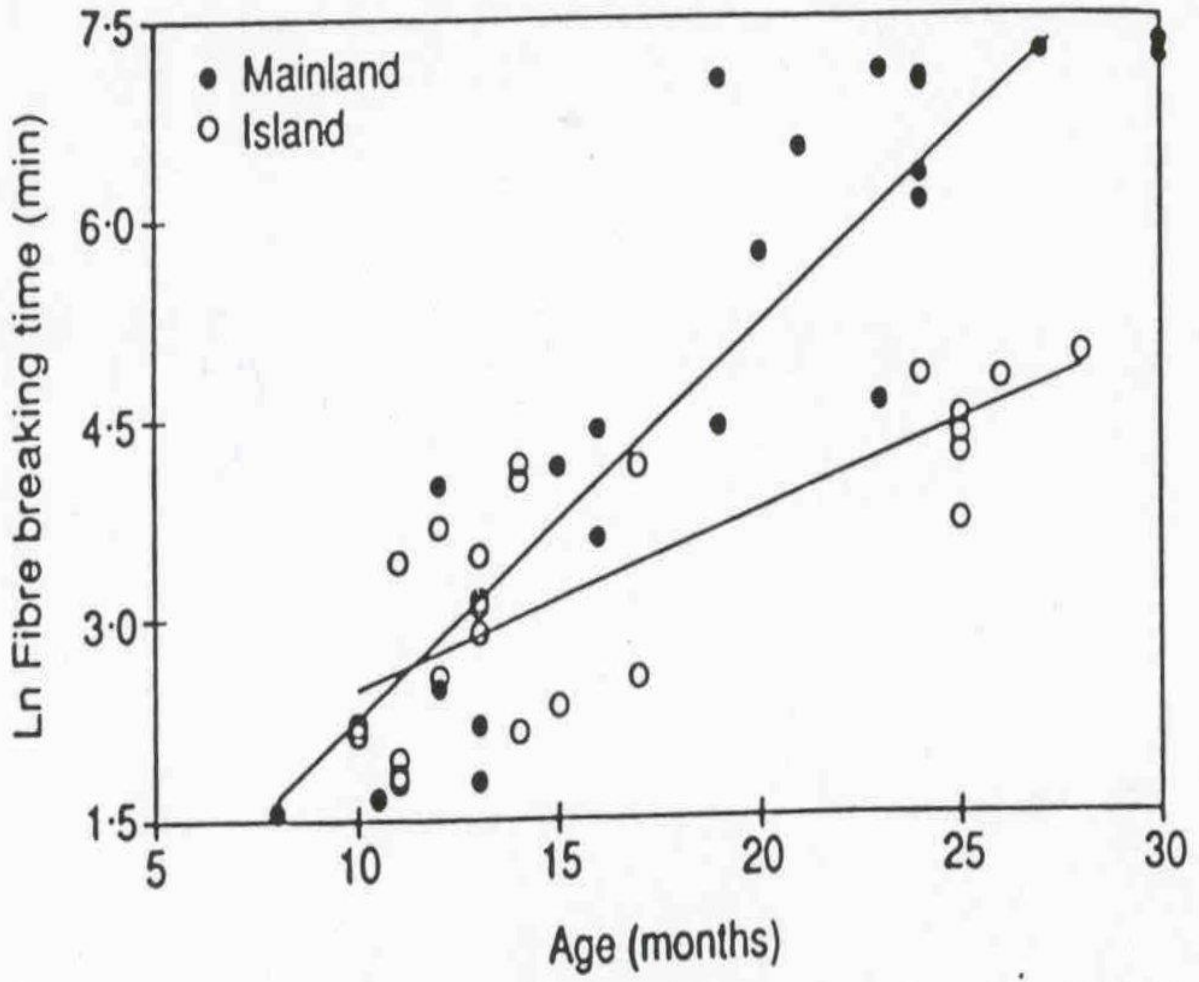


FIG. 3. Tail tendon fibre breaking time. Each point represents the mean breaking time of two to four fibres. The regression slopes are both significant at $P < 0{\cdot}001$ and the lines are significantly different ($F_{2,43} = 19{\cdot}312$, $P \ll 0{\cdot}001$).

Ln = natural logarithm

Questions?

Cellular Theories of Aging (bottom up)

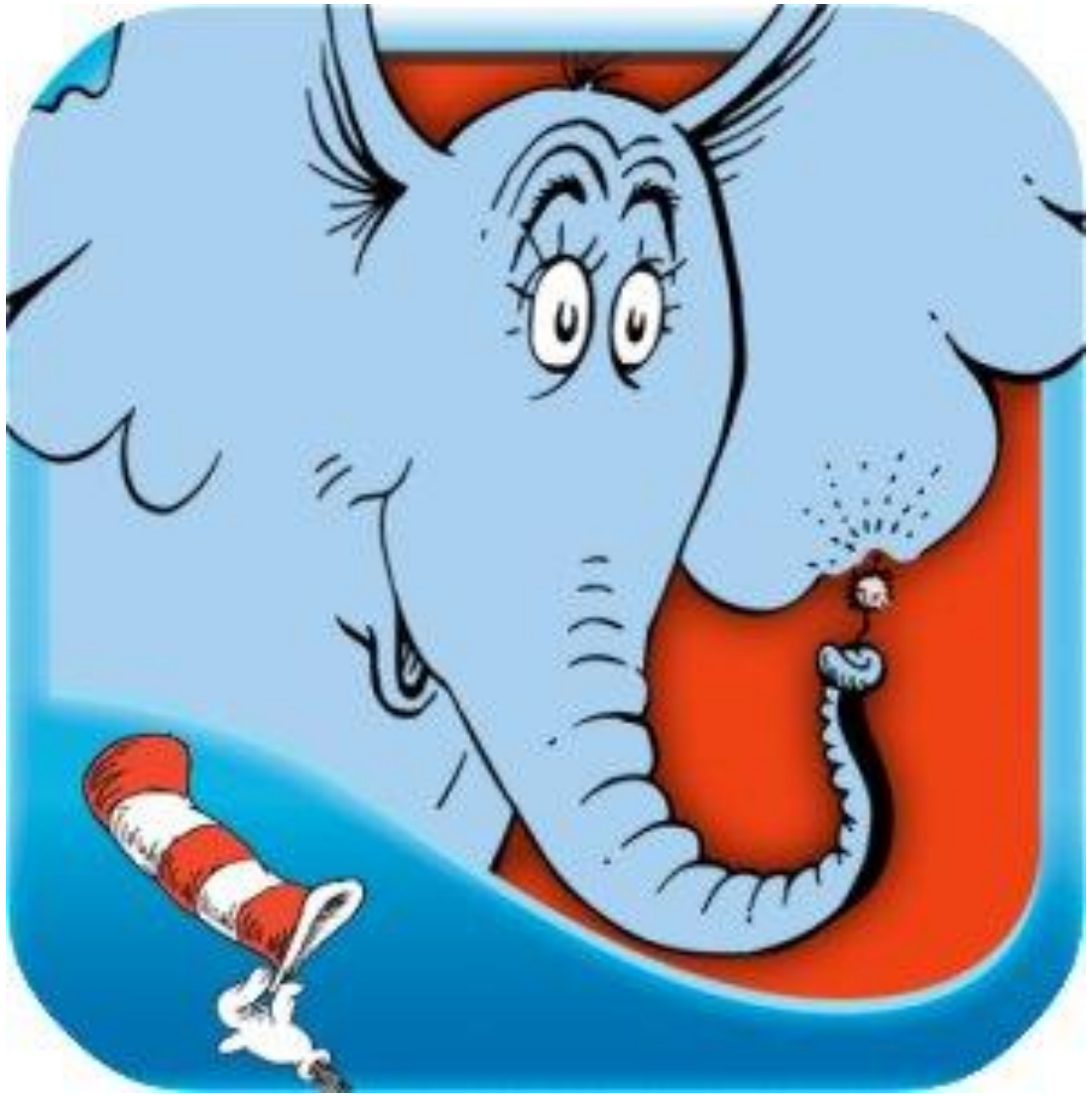
- Cellular theories hold that aging begins within cells and eventually affects the entire organism.

Understanding the Cell

Anything that happens within an organism does so because a cell does something.

Therefore, understanding cells is key to understanding cell theories of anything, including aging.

Of Cells, Horton and Whoville



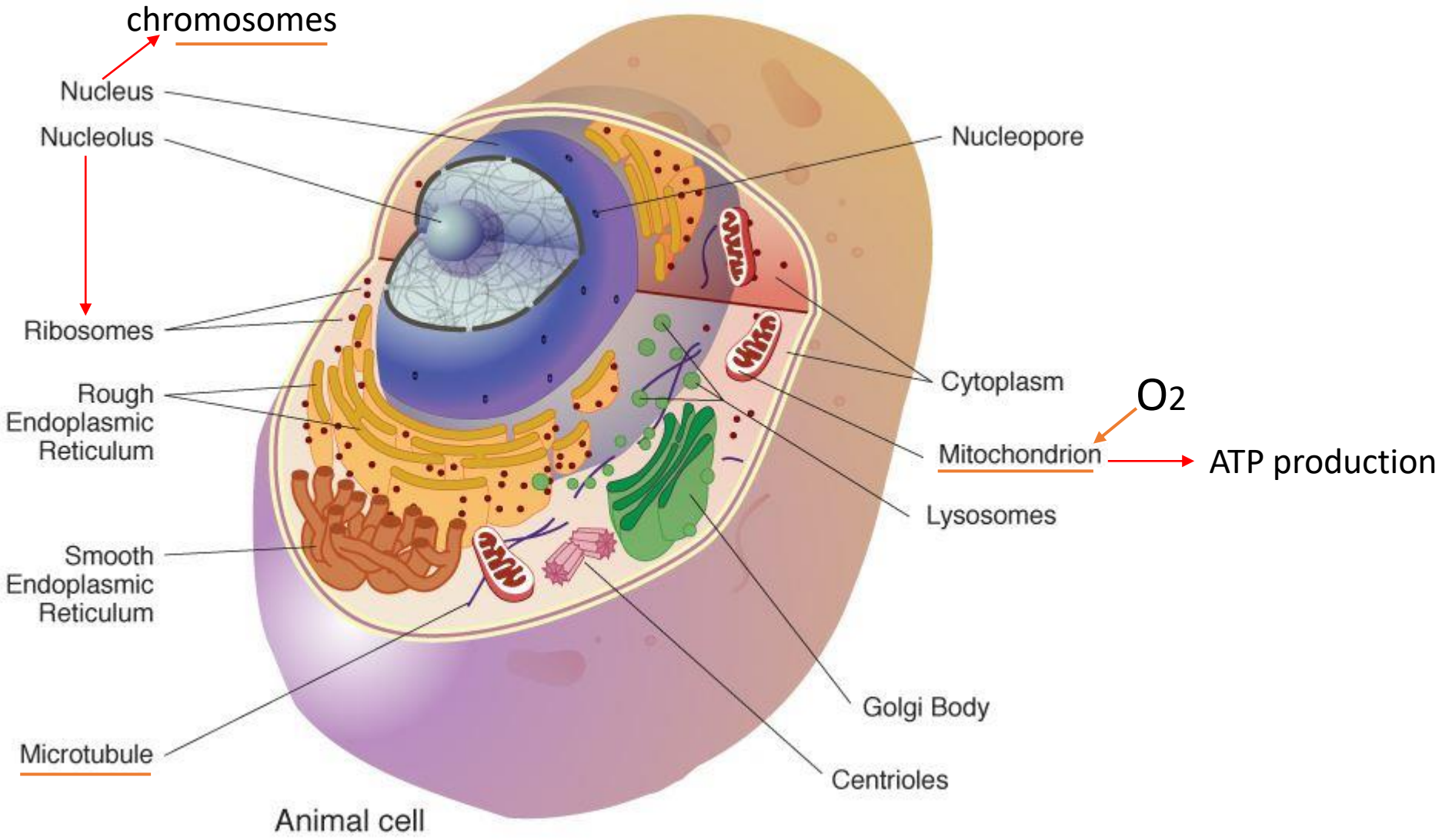
Dr. Seuss's story of *Horton Hears a Who* reminds us that micro-worlds exist within the bounds of macro-worlds.

With this in mind, a cell is to a person what Whoville is to Horton's world.

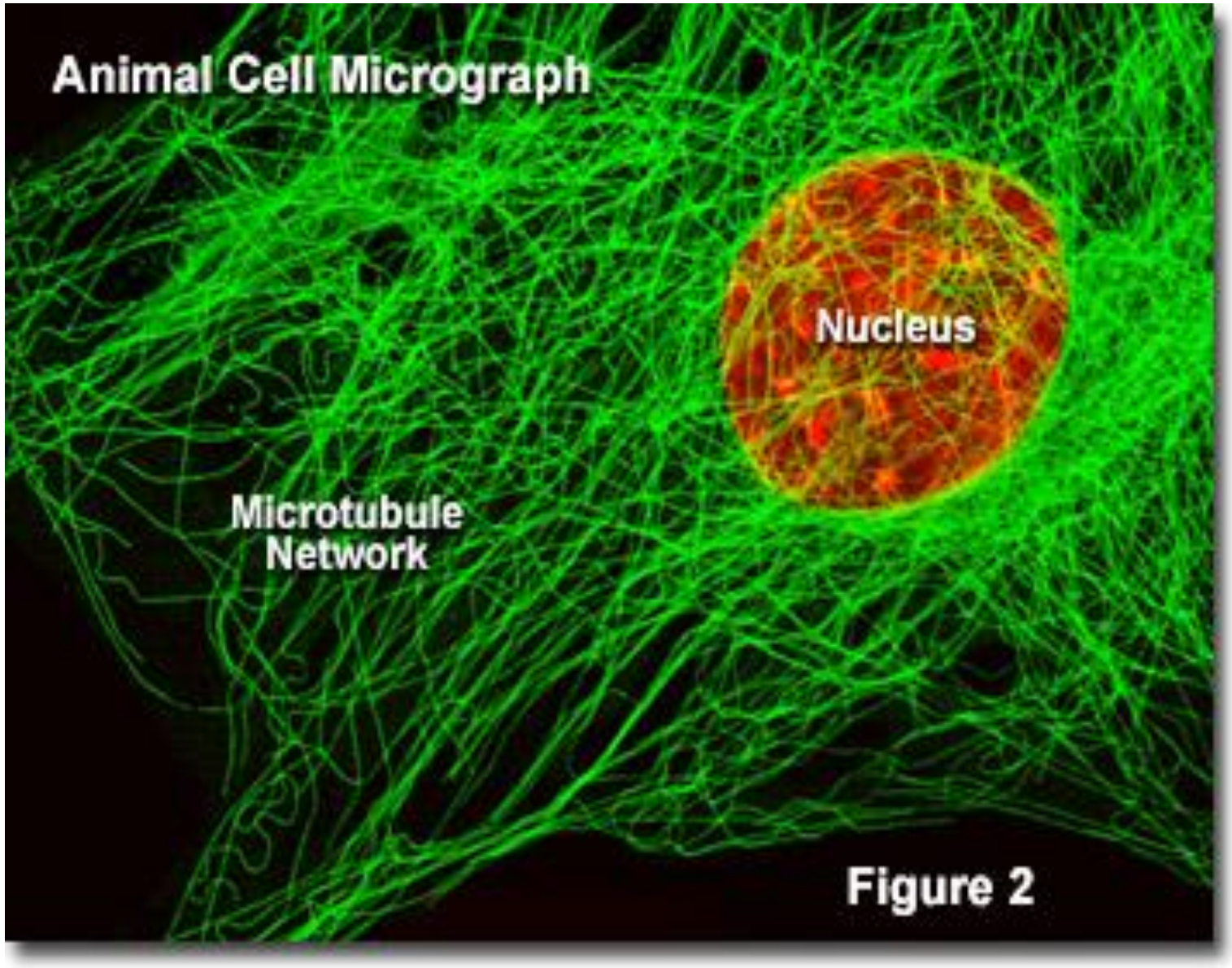
Cells are, in fact, micro-organisms complete with their own internal structure.

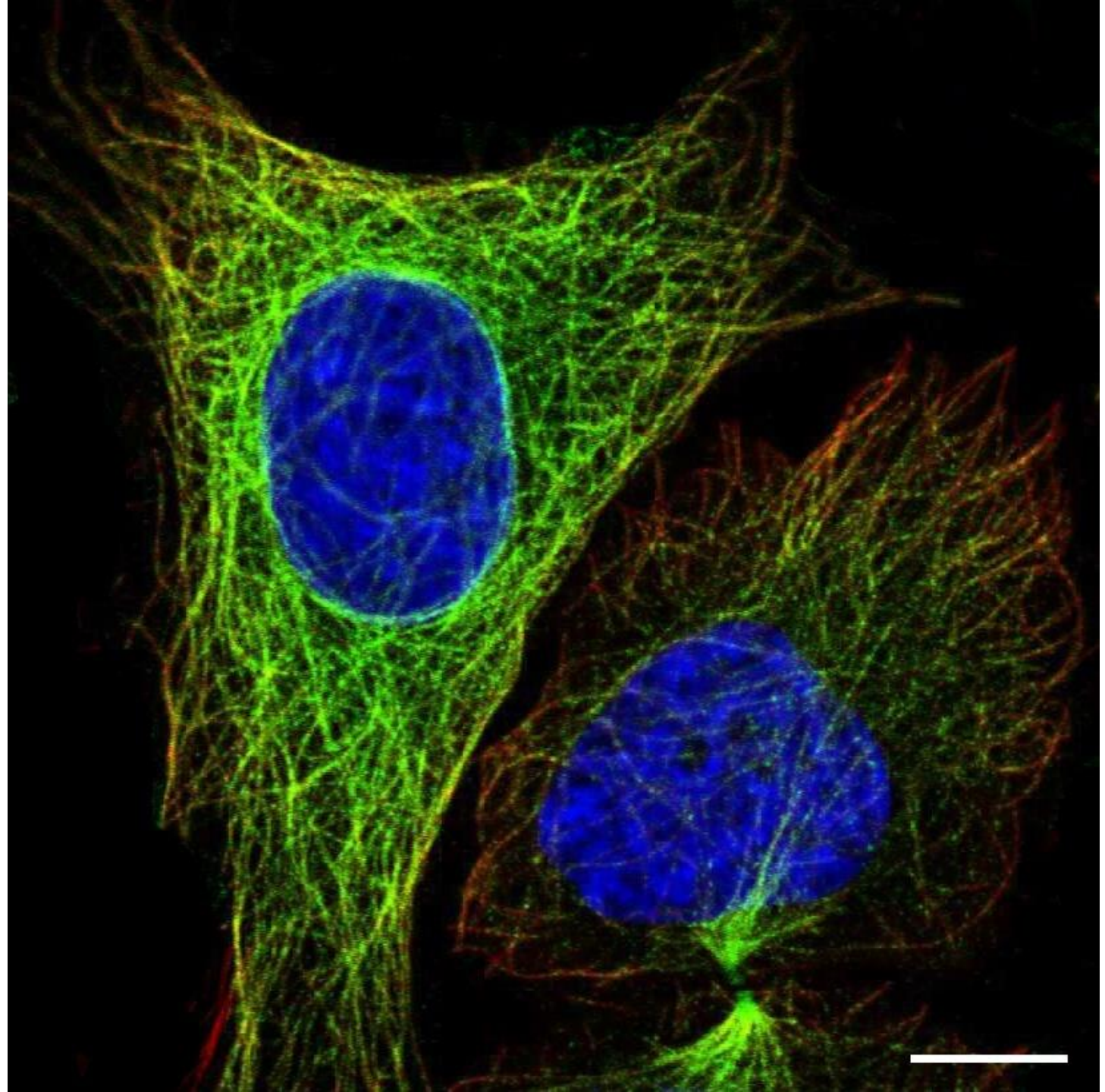
And, cells age resulting in the aging of organisms.

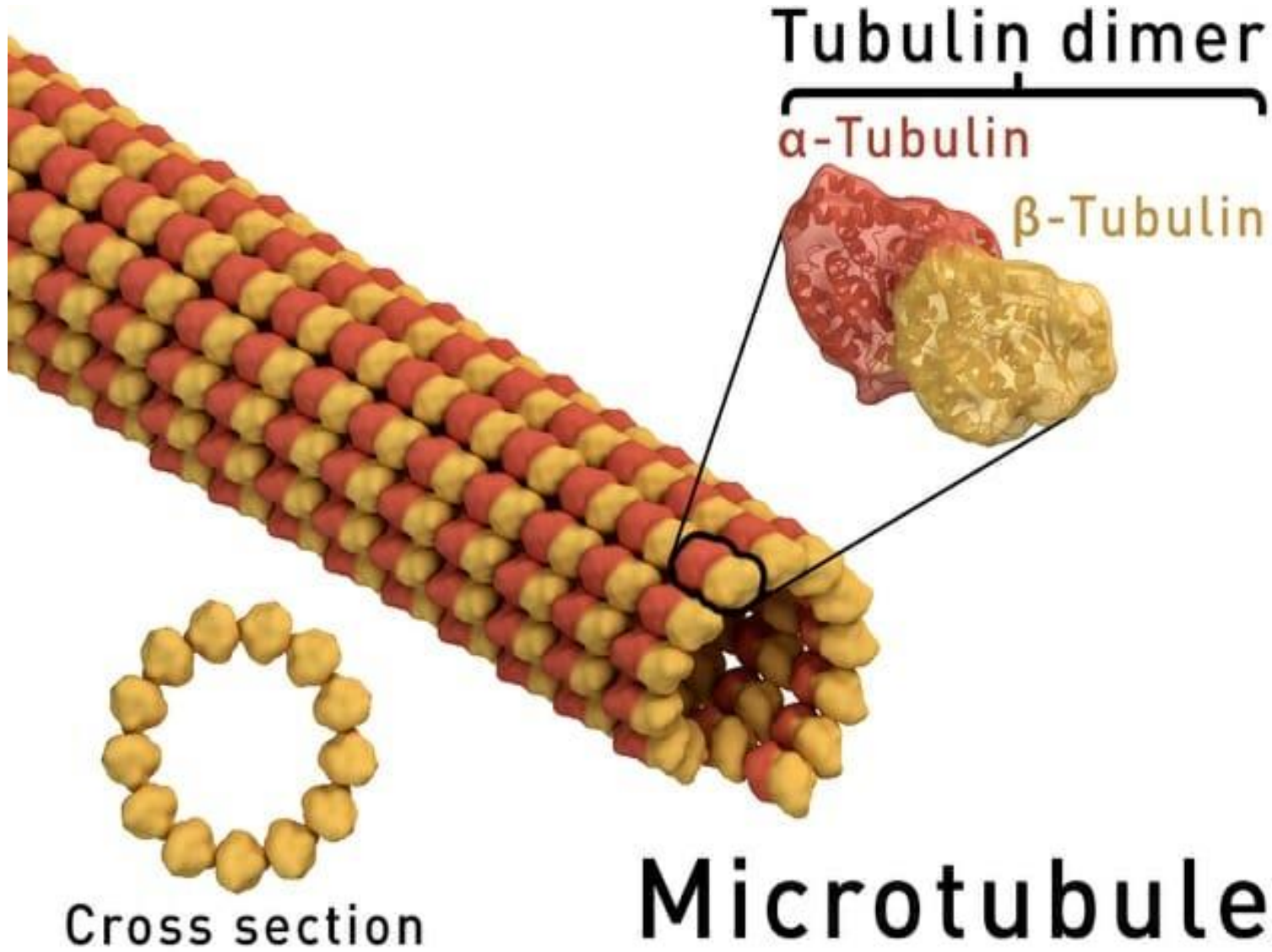
General structure of an eukaryotic (animal) cell (organelles = tinny organs = component parts of a cell)



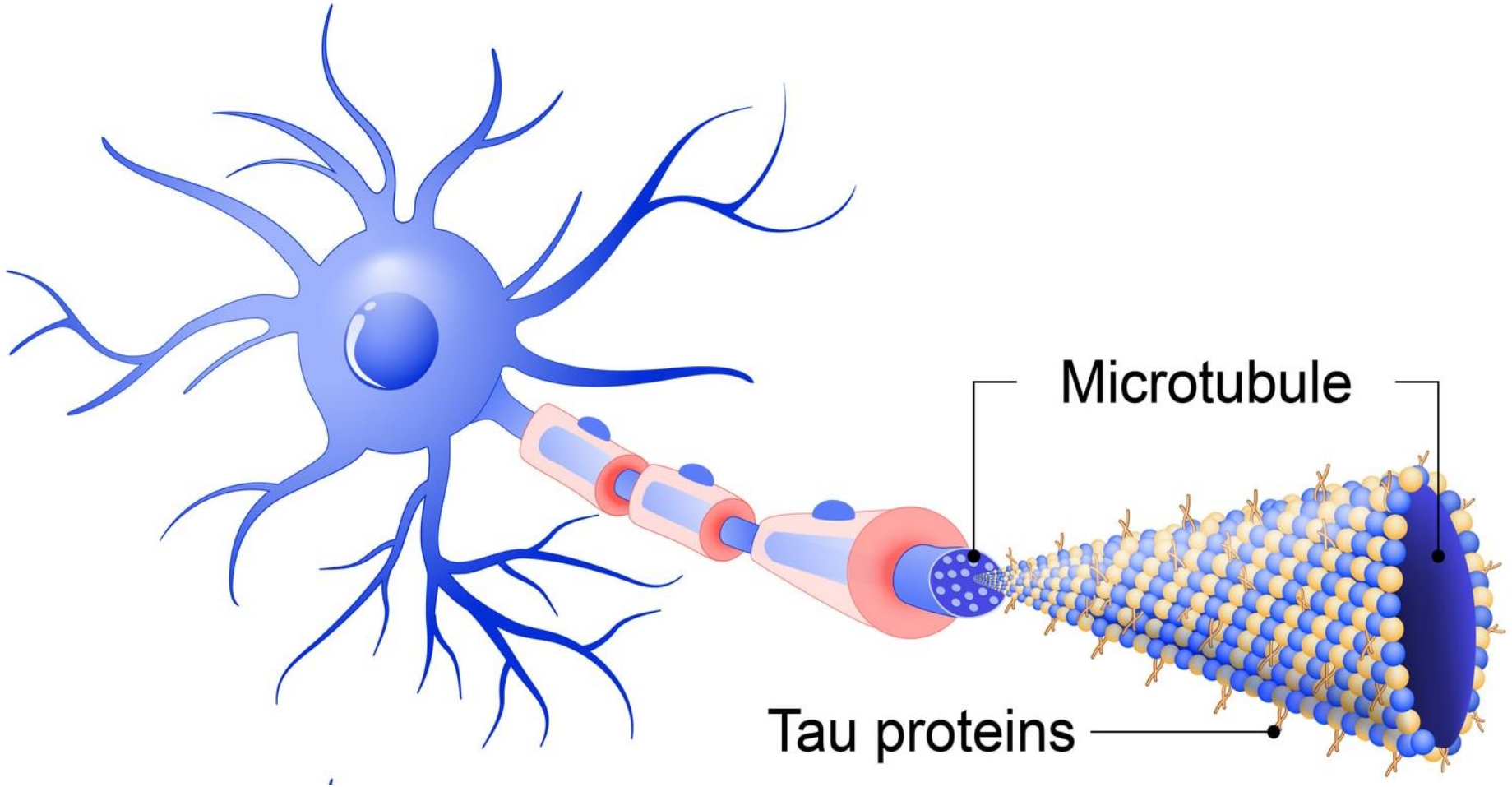
Microtubules – the transportation channels within a cell






Tubulin dimer
α-Tubulin
β-Tubulin
Cross section
Microtubule

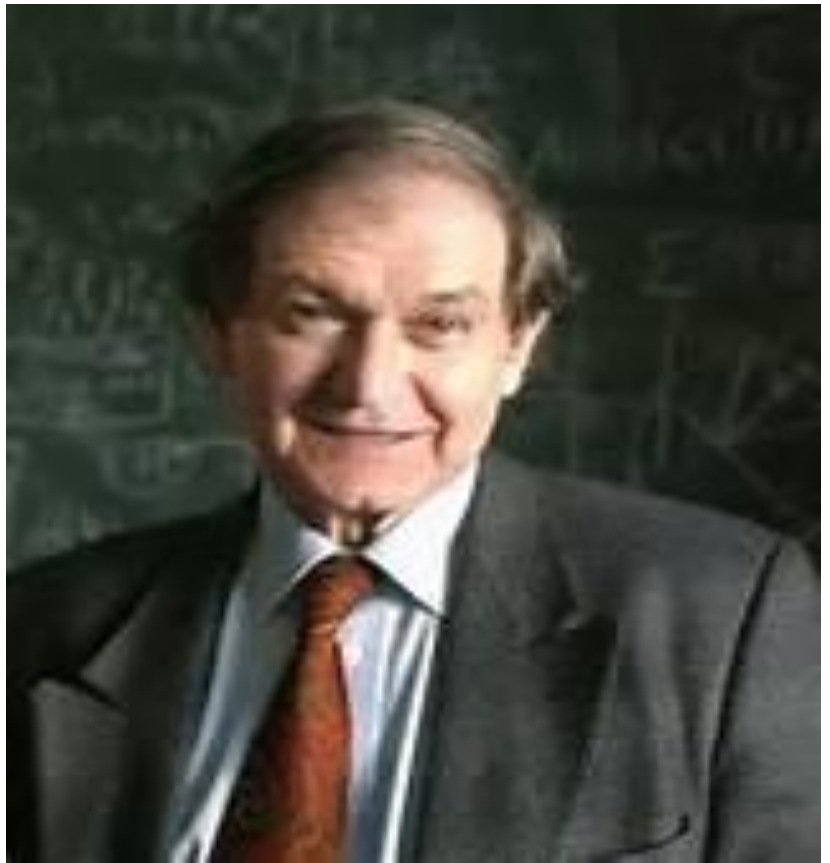
Microtubules transmit information along neurons (nerve cells)



Quantum vibrational computations in neural microtubules orchestrate consciousness.

Stuard Hammeroff, Univ. of Arizona

Sir Roger Penrose, Oxford Univ.

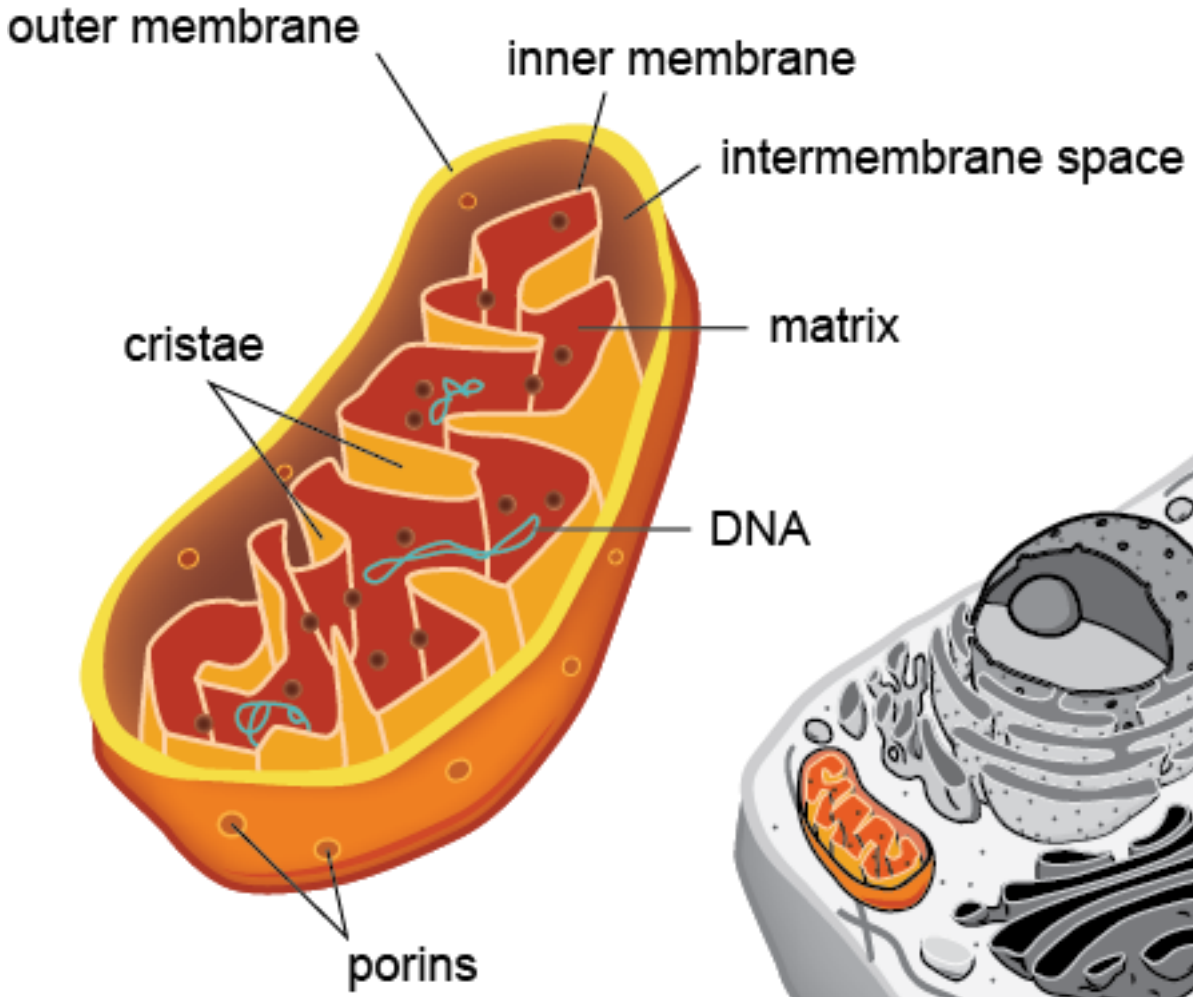


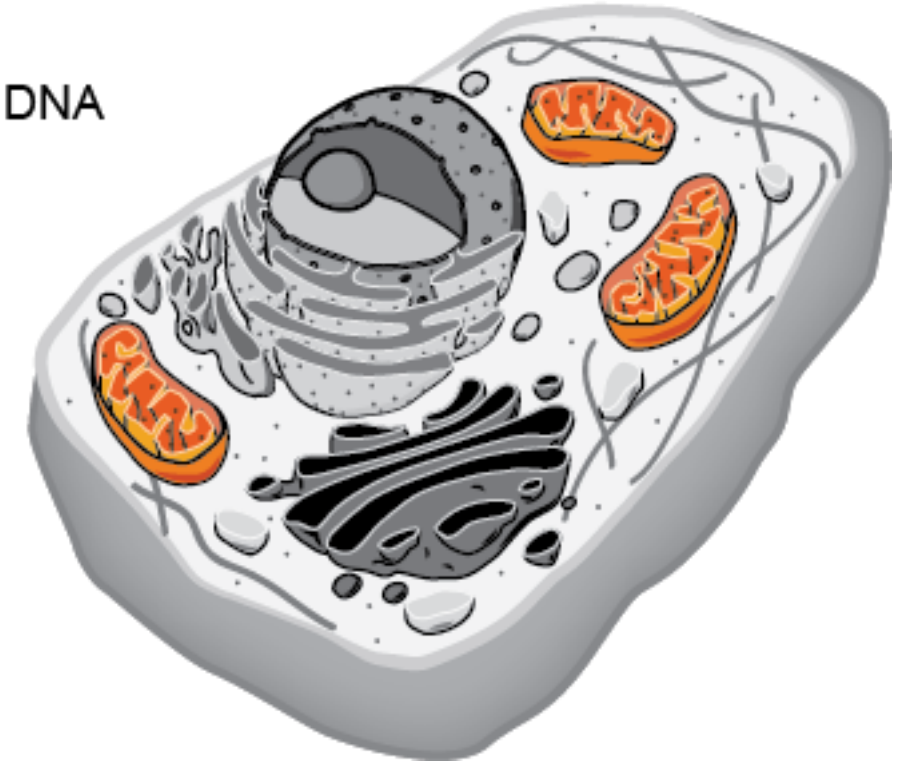
Human functions that most likely act by quantum means:
(All are affected by aging)

- Vision
- Hearing
- The action of antibodies
- DNA directed synthesis of proteins
  - aka genetic expression

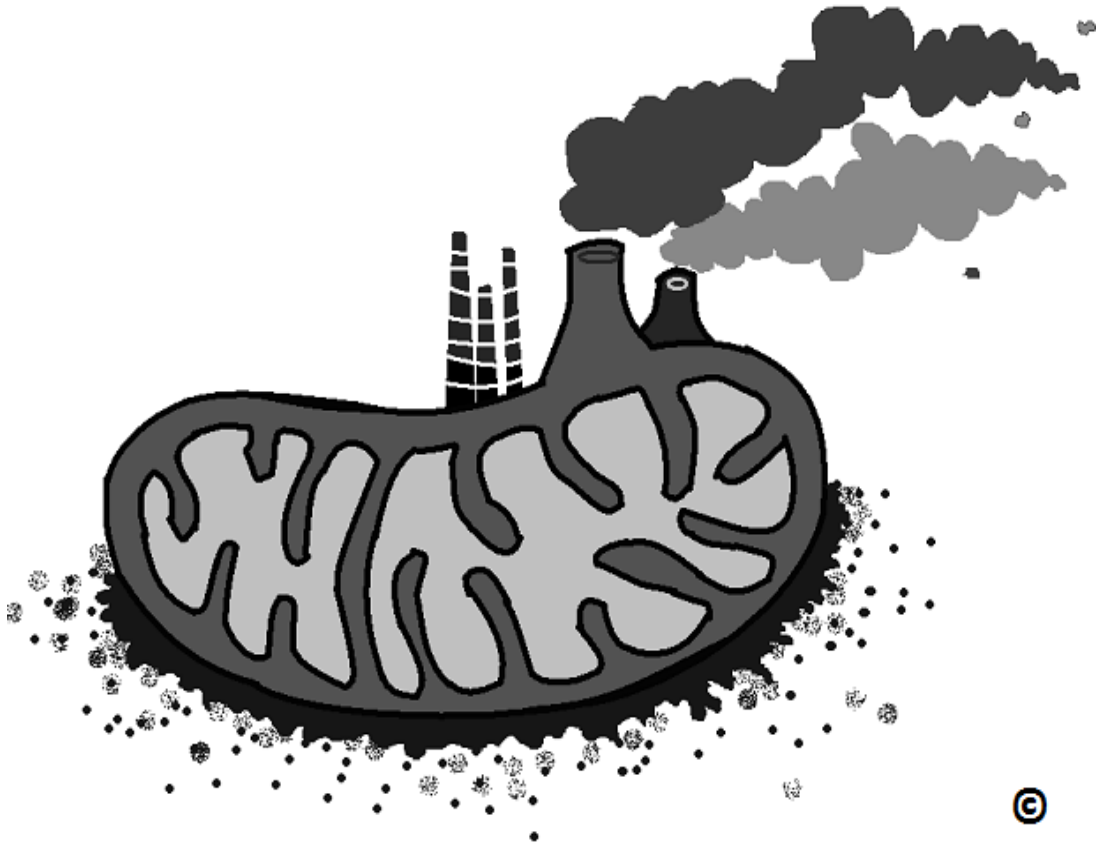
Questions?

Mitochondria: The organelles that produce adenosine triphosphate (ATP)





Like factories that emit pollutants, mitochondria emit damaging byproducts during the production of ATP



ATP

↑

- Mitochondria ← O_2

↓

- Oxygen free radicals
- (a.k.a. oxidants)

↓

- Cell damage

↓

- aging

Stress, oxidative damaging and aging

Stress (physical or mental)

↓

Physiological stress response

↓

Increased oxygen consumption

↓

Oxygen free radical

↓

Oxidative damage

↓

Aging

Radical: “*Marked by a considerable departure from the usual or traditional*” – Merriam Webster

What is an oxygen free radical?

(aka oxygen radical, aka free radical)

During the use of oxygen to make ATP,
the some of the electrons are lost as oxygen splits into single atoms.

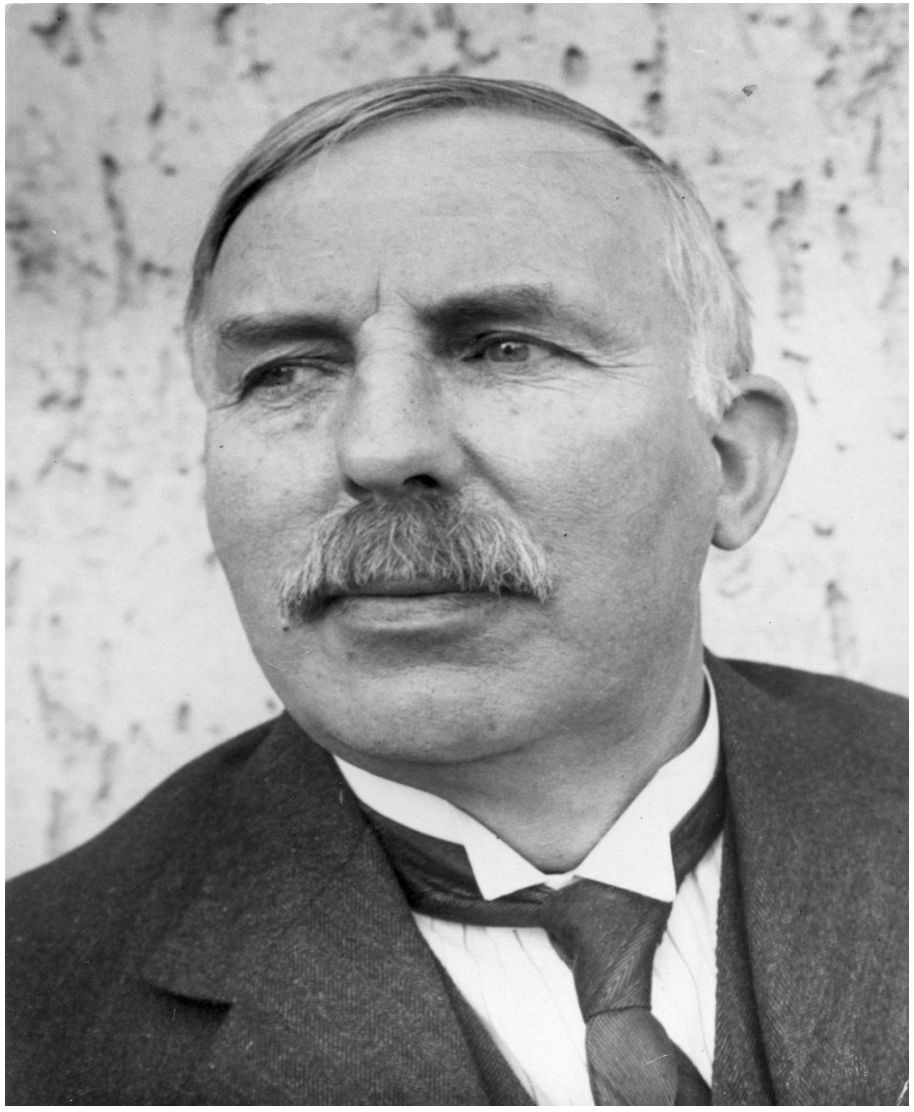
These electron deficient atoms, are called free radicals.

Free radicals scavenge the body to grab electrons from other molecules.

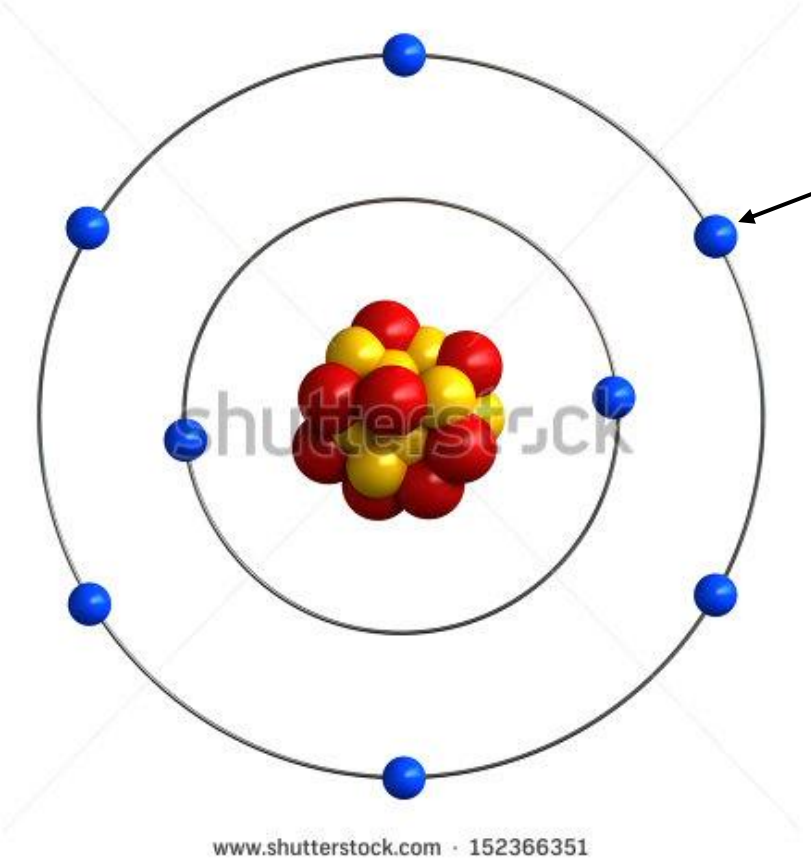
This process reforms the proper number of oxygen electrons.

Such action can damage any and all parts of a cell.

New Zeeland physicist Ernest Rutherford - Orbital model of an atom (1911)

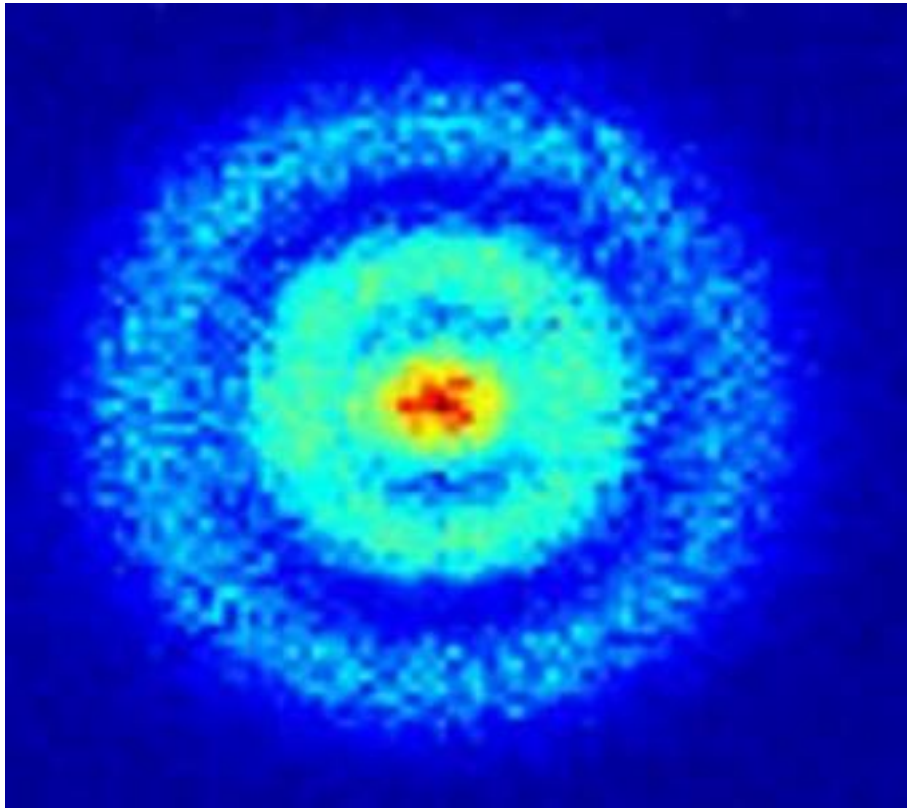


Orbital model of the oxygen atom



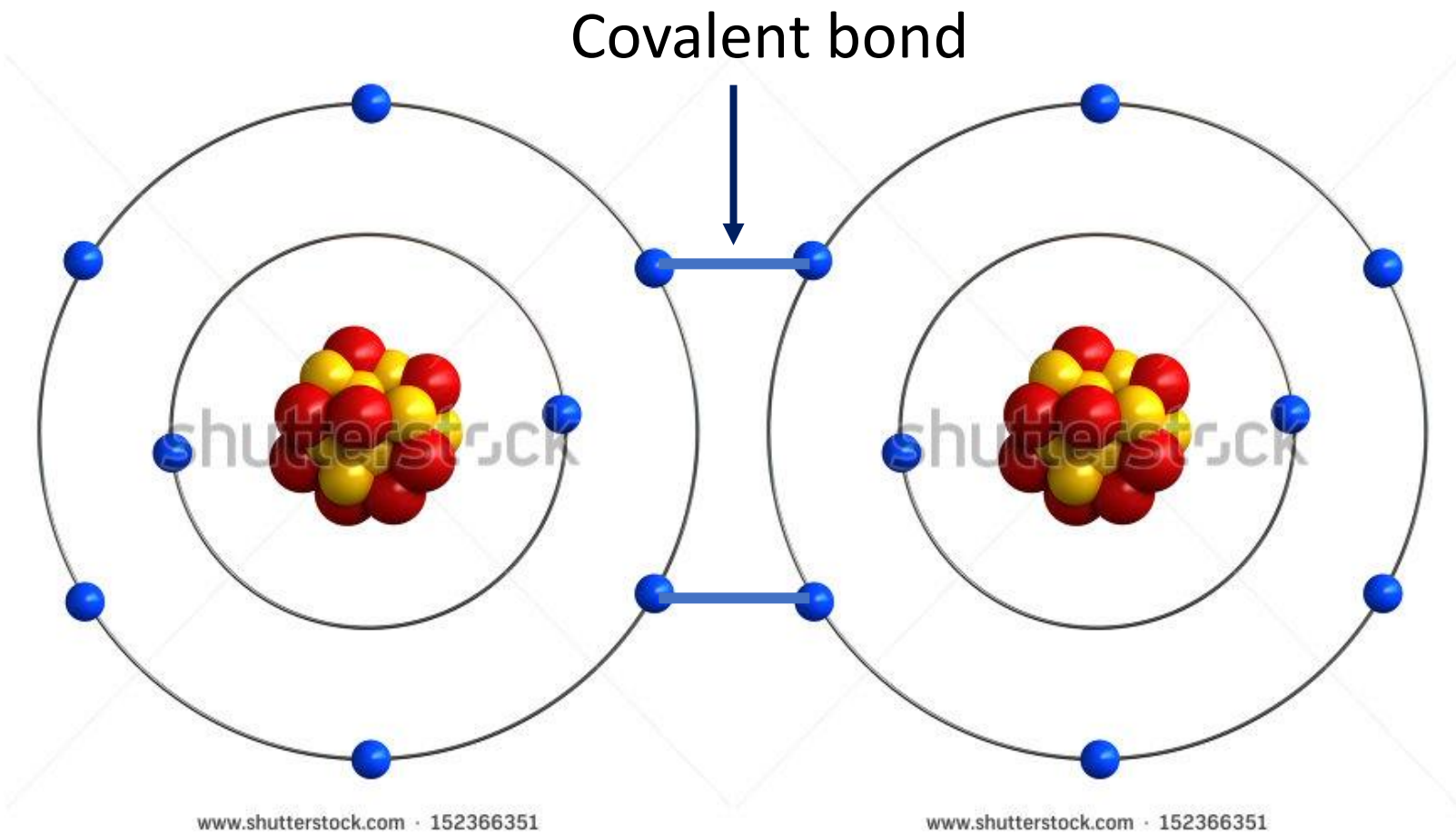
Electrons within atoms exist in spread out energy states.

Quantum micrograph of an atom (circa 2013)

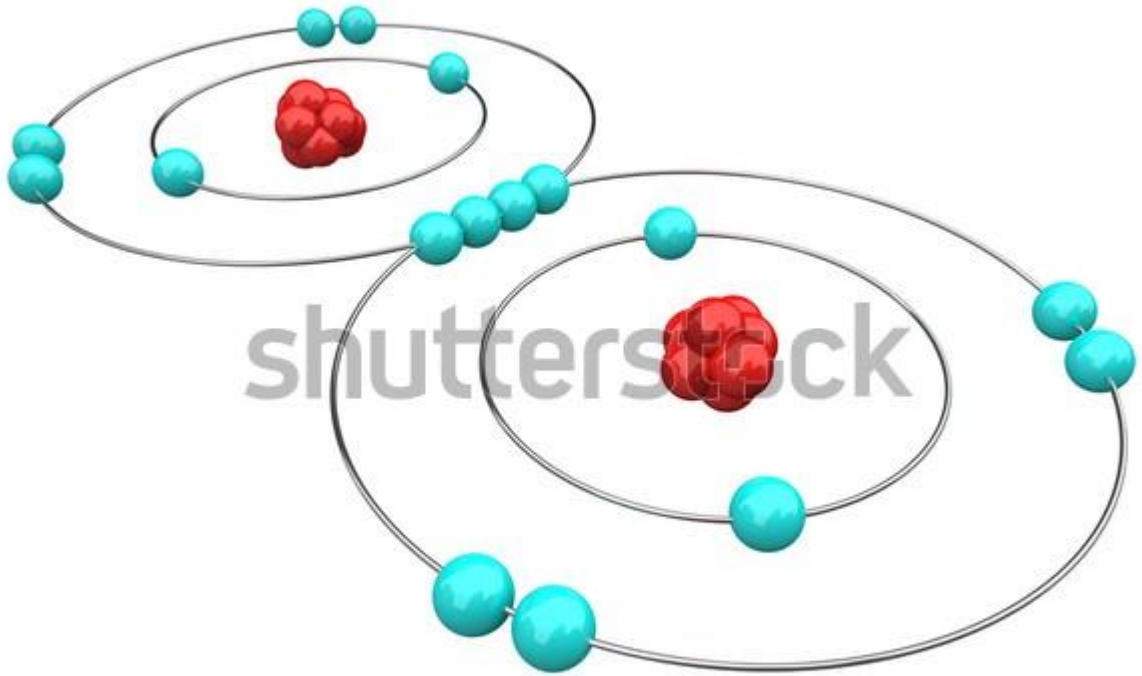


For structure and function of atoms:
The Great Courses: “*Understanding the Quantum World*”, Erica Carlson

Molecular oxygen (O_2)

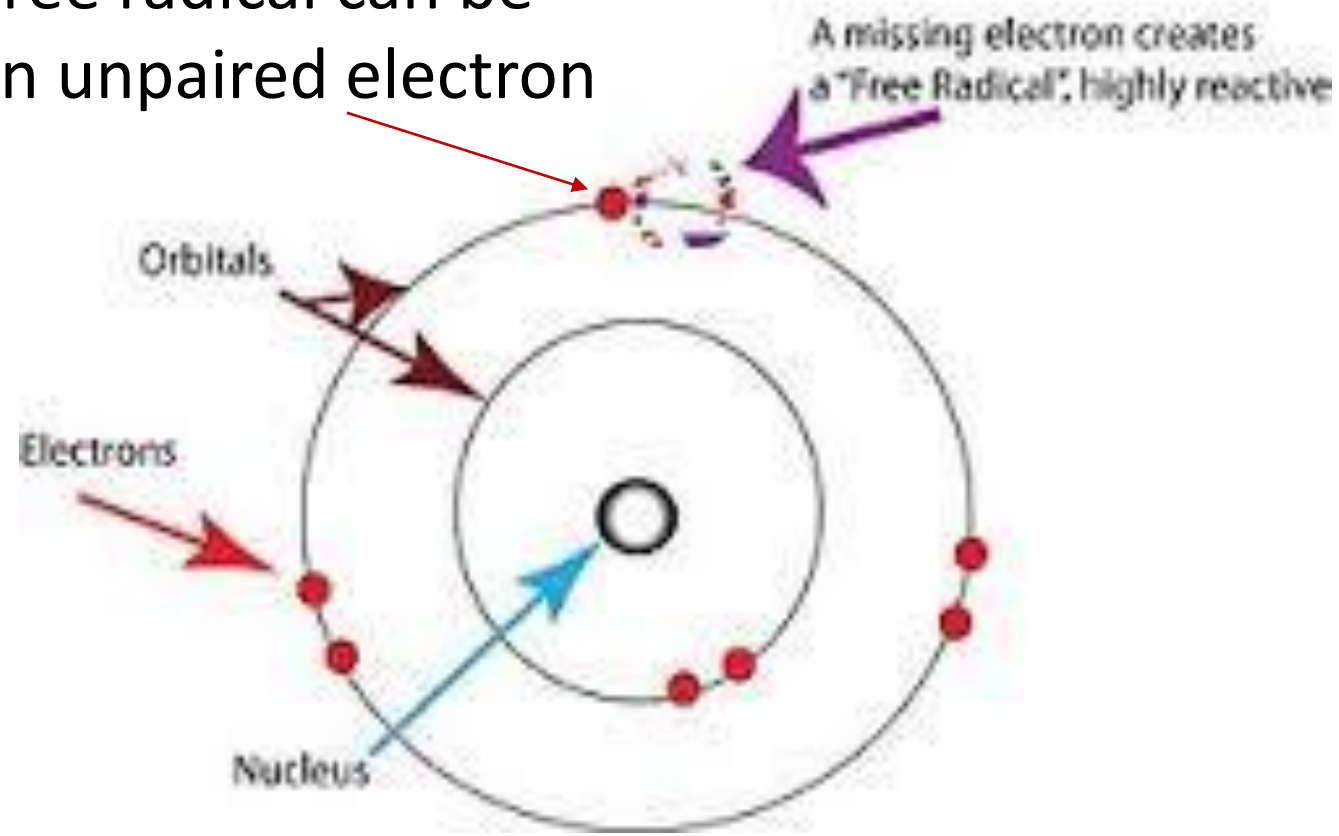


The oxygen molecule
Electron sharing gives stability to the atoms



An oxygen free radical

An oxygen free radical can be viewed as an unpaired electron



The superoxide molecule

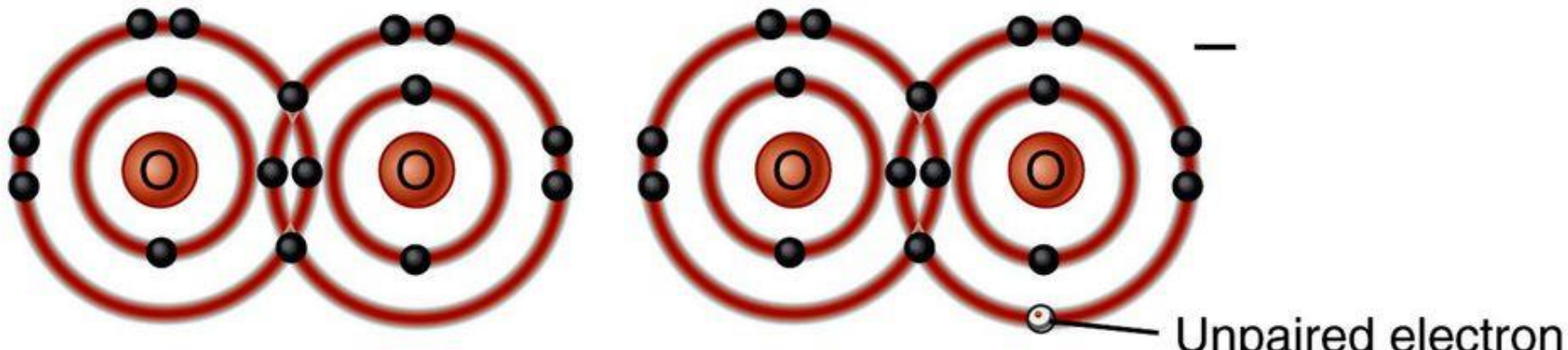
In addition to an electron deficient atom creating a free radical,

The oxygen molecule (O_2) can pick up an electron

It then becomes a superoxide molecule.

An oxygen molecule with an extra (unpaired) electron.

Figure 2.3 Atomic structures of an oxygen molecule and a superoxide molecule



(a) Oxygen molecule (O_2) (b) Superoxide free radical (O_2^-)

Figure 02.03 Tortora - PAP 12/e

What oxygen radicals and the superoxide molecule have in common is:

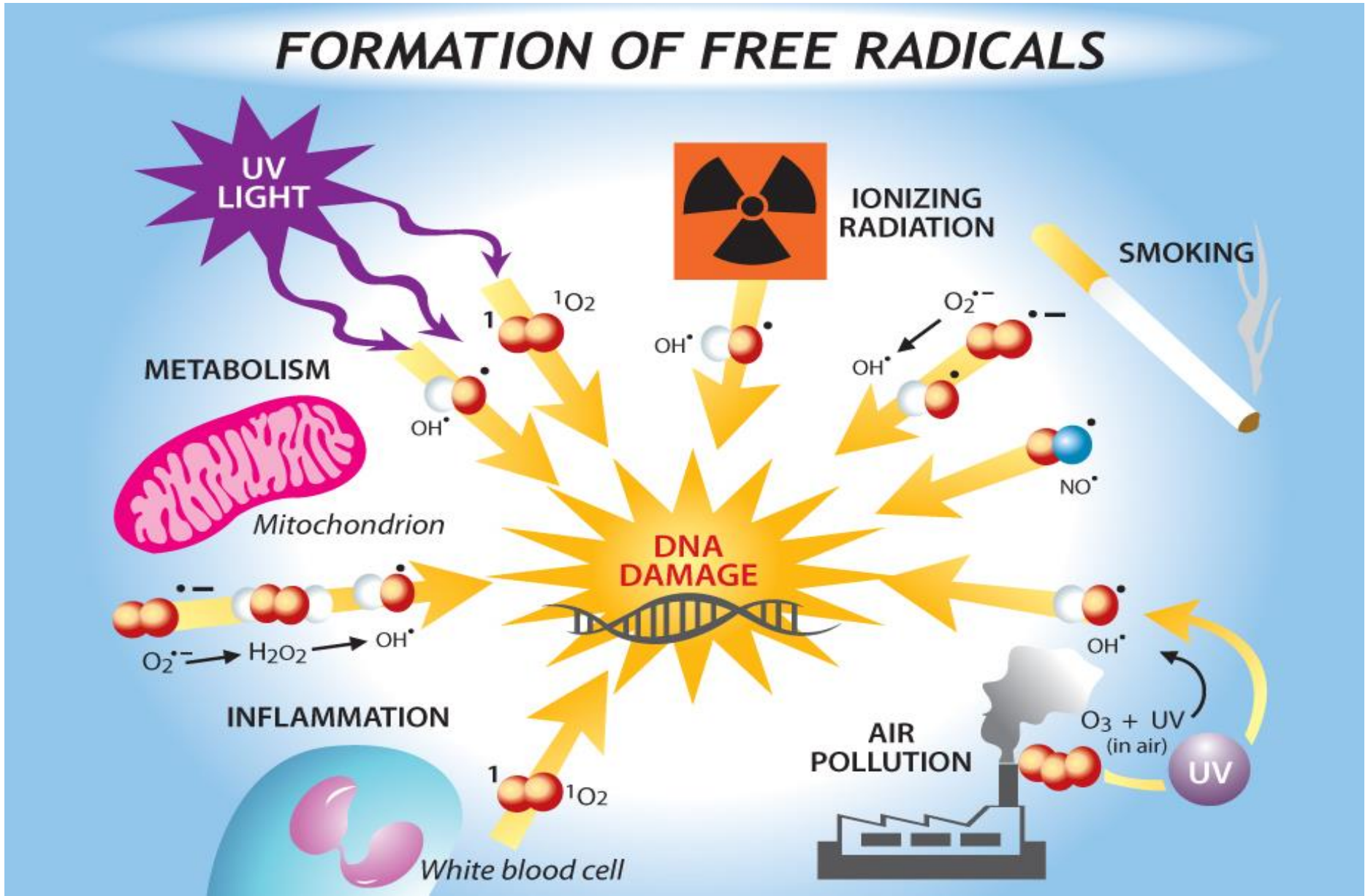
An unpaired electron in the outer (valence) orbit.

Both are highly reactive and damaging.

The term “oxygen radical” normally includes the superoxide molecule

Denham Harman: Biogerontologist , Univ Calif Berkley
Developed oxygen free radical theory of aging (circa 1960)

Oxygen Radical = Free Radical = Oxygen Free Radical



Stress, oxidative damaging and aging

Stress (physical or mental)

↓

Physiological stress response

↓

Increased oxygen consumption

↓

Oxygen free radical

↓

Oxidative damage

↓

Aging

Questions?

Oxidative damage of cells mainly occurs by damage of genes on DNA

A major mechanism of cellular aging

A gene is a section of DNA that codes for the manufacture of a protein.

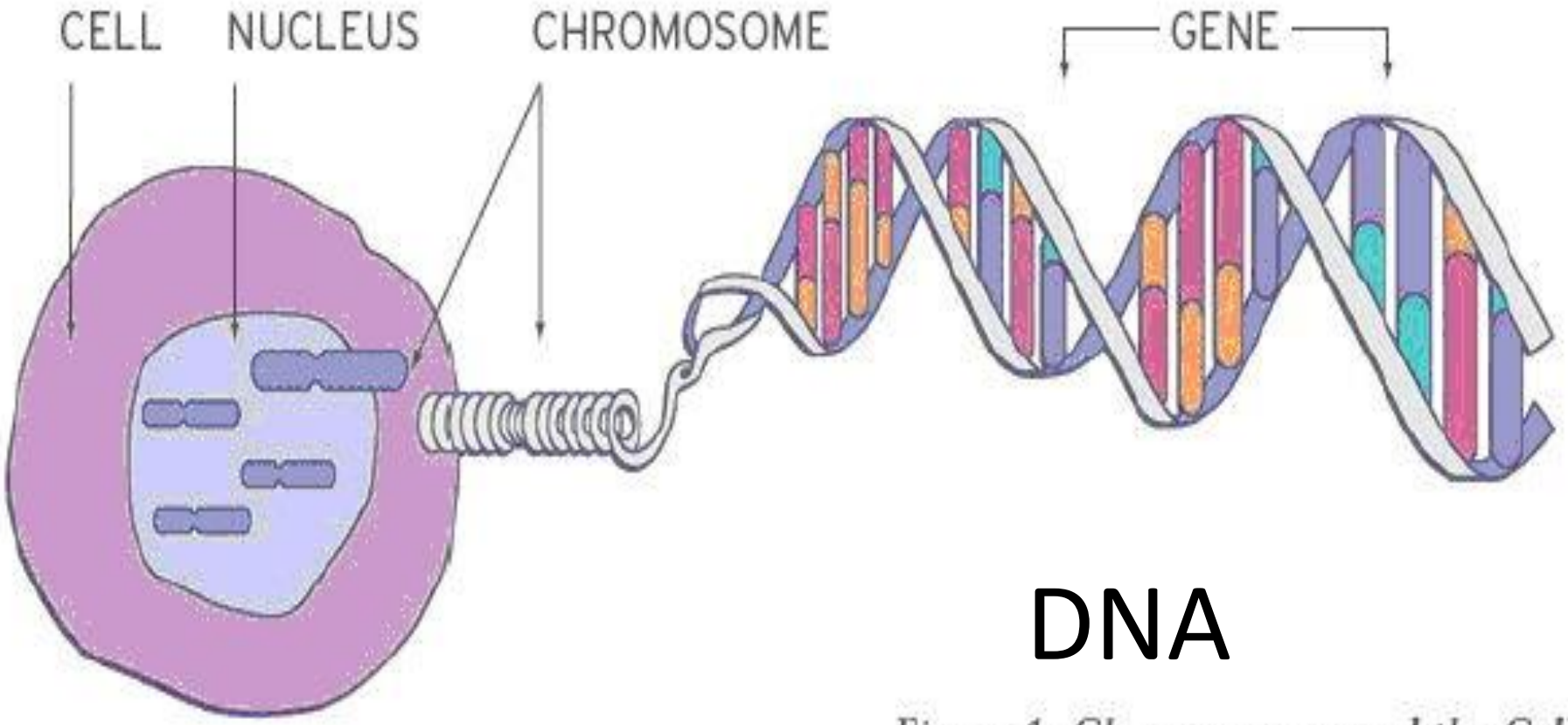
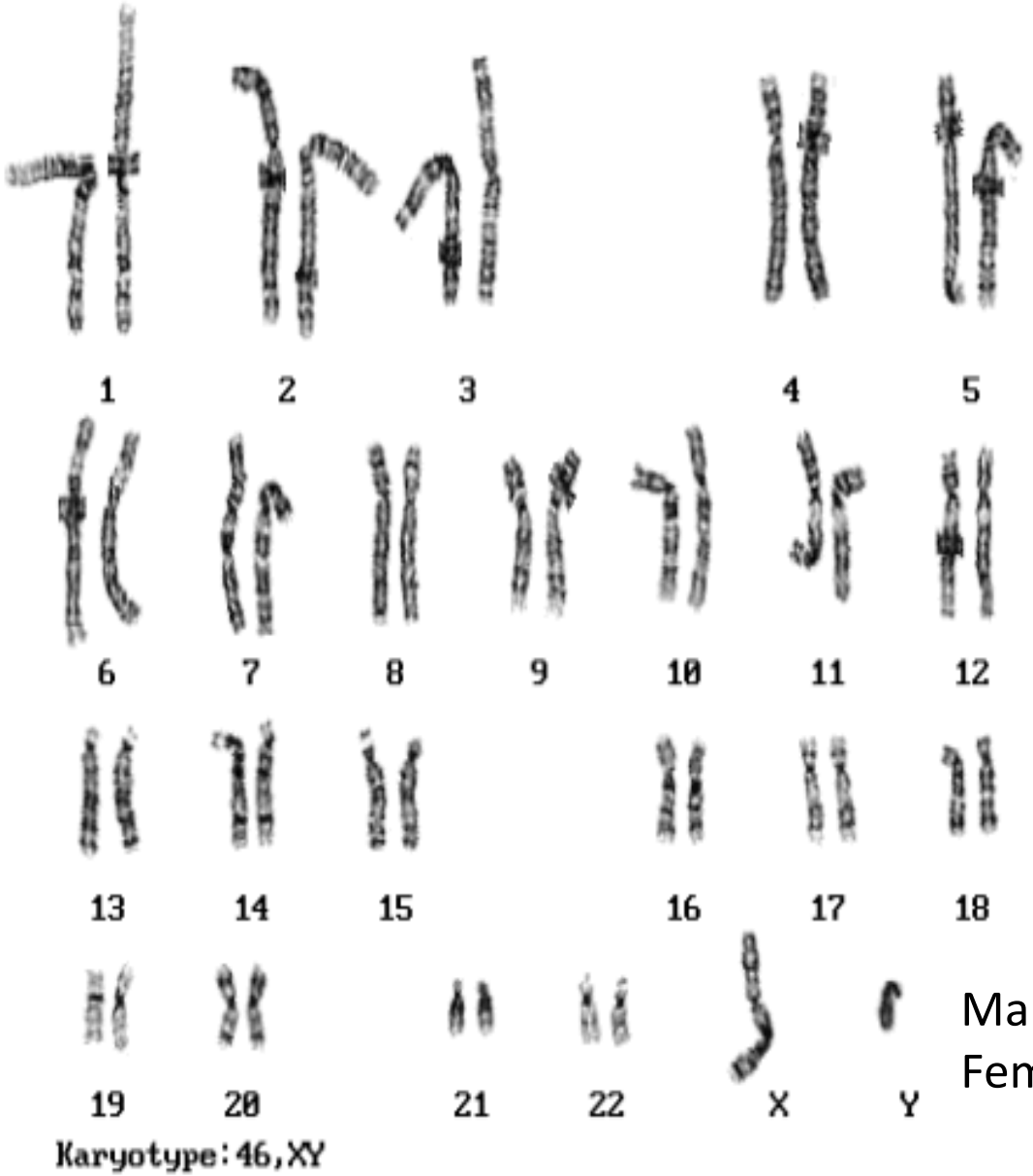


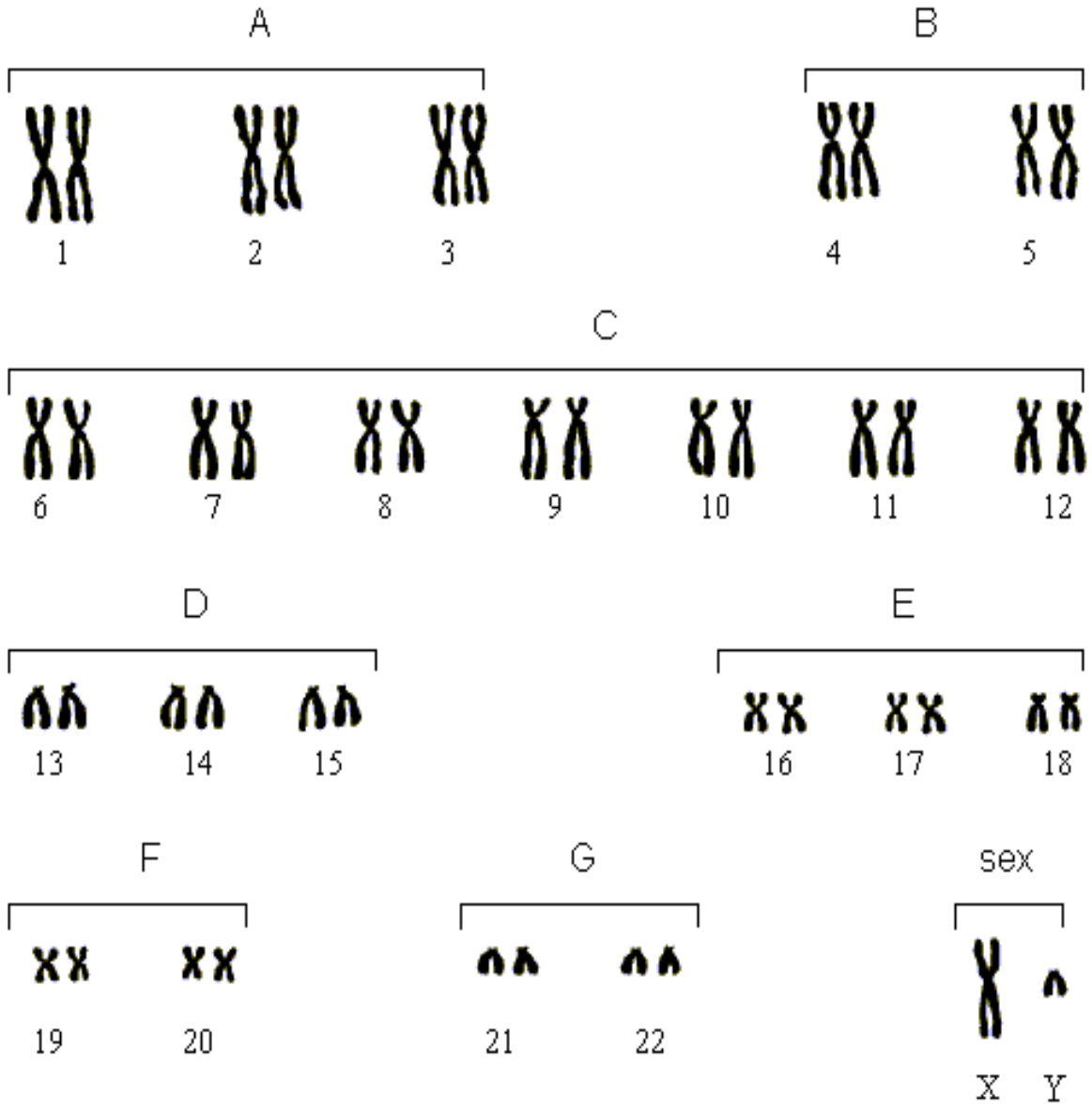
Figure 1: Chromosomes and the Cell

human chromosomes



Male = XY
Female XX

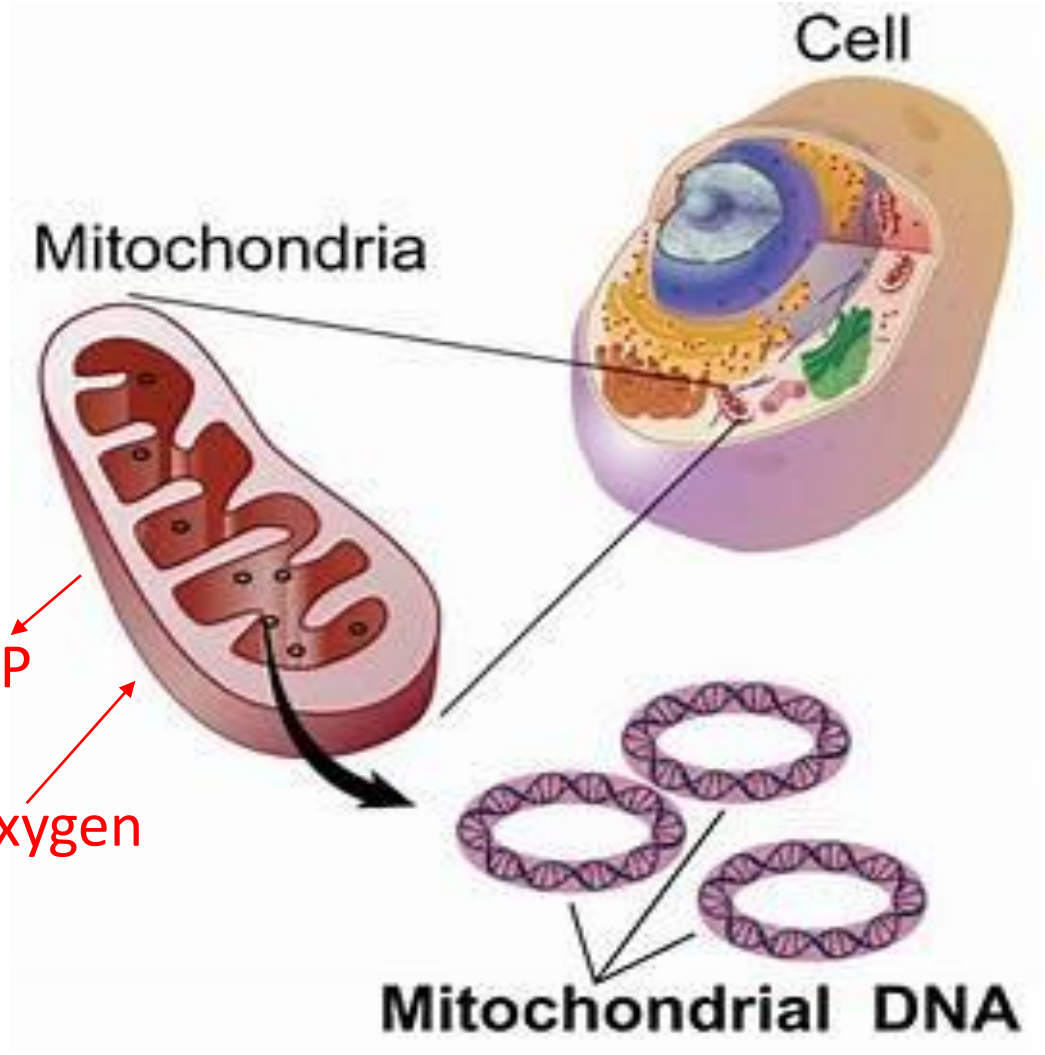
Chromosomes are more easily viewed just before cell division



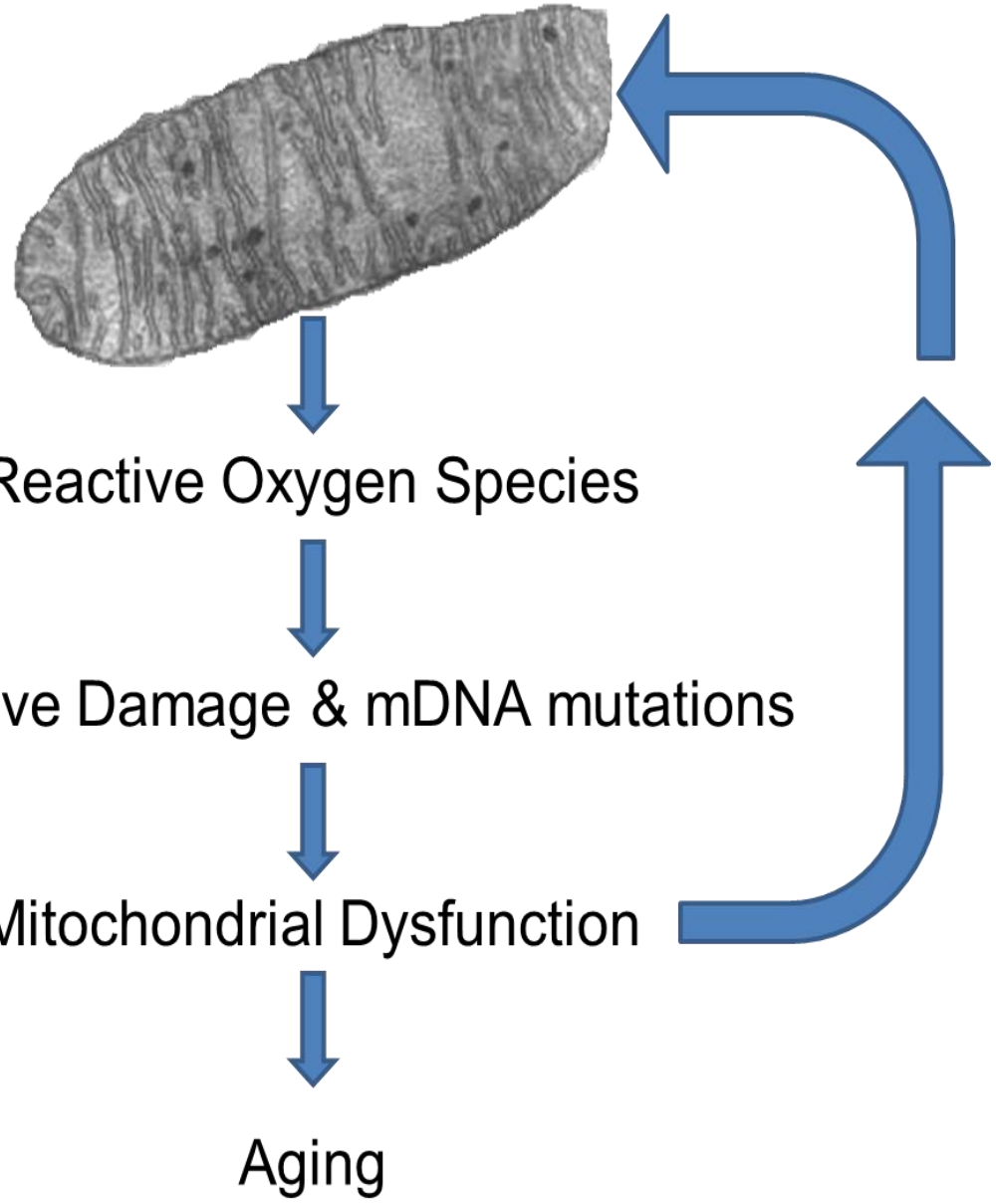
Reduced DNA Redundancy:
A factor in the role of genetic damage with aging.

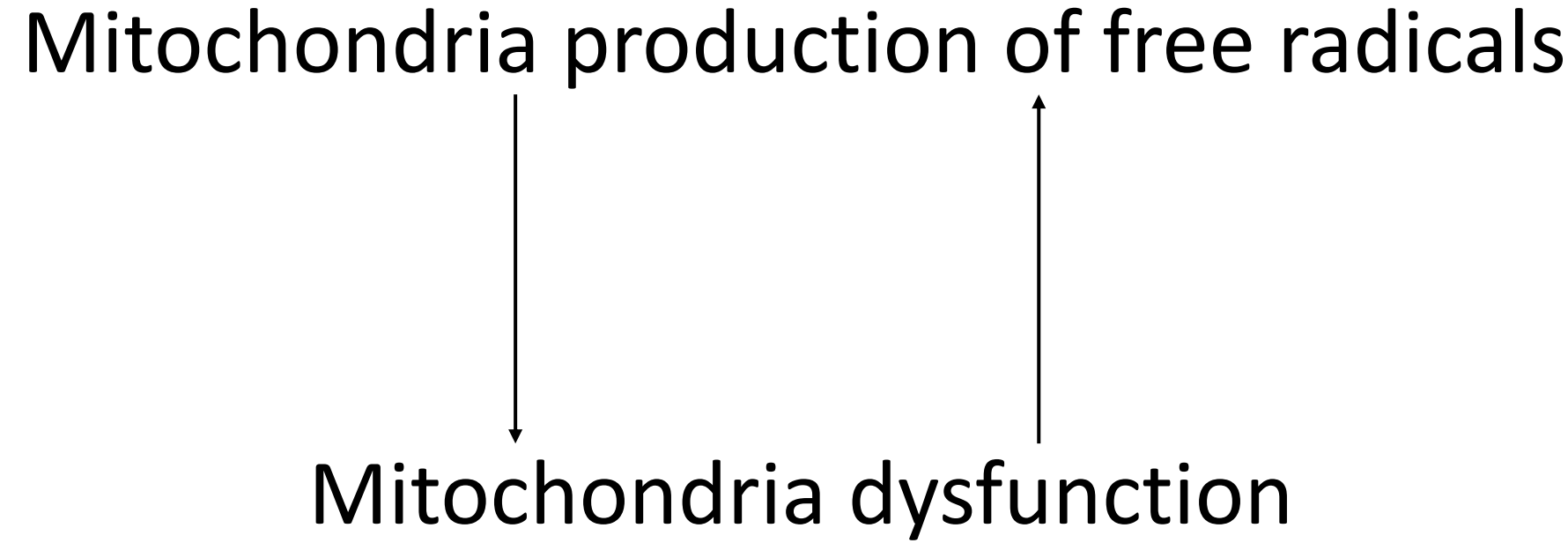
- As an organism ages its DNA reserves are used up and remaining DNA is more likely to be damaged.

Oxidative damage of DNA includes mitochondria DNA



Three chromosomes each with 13 genes

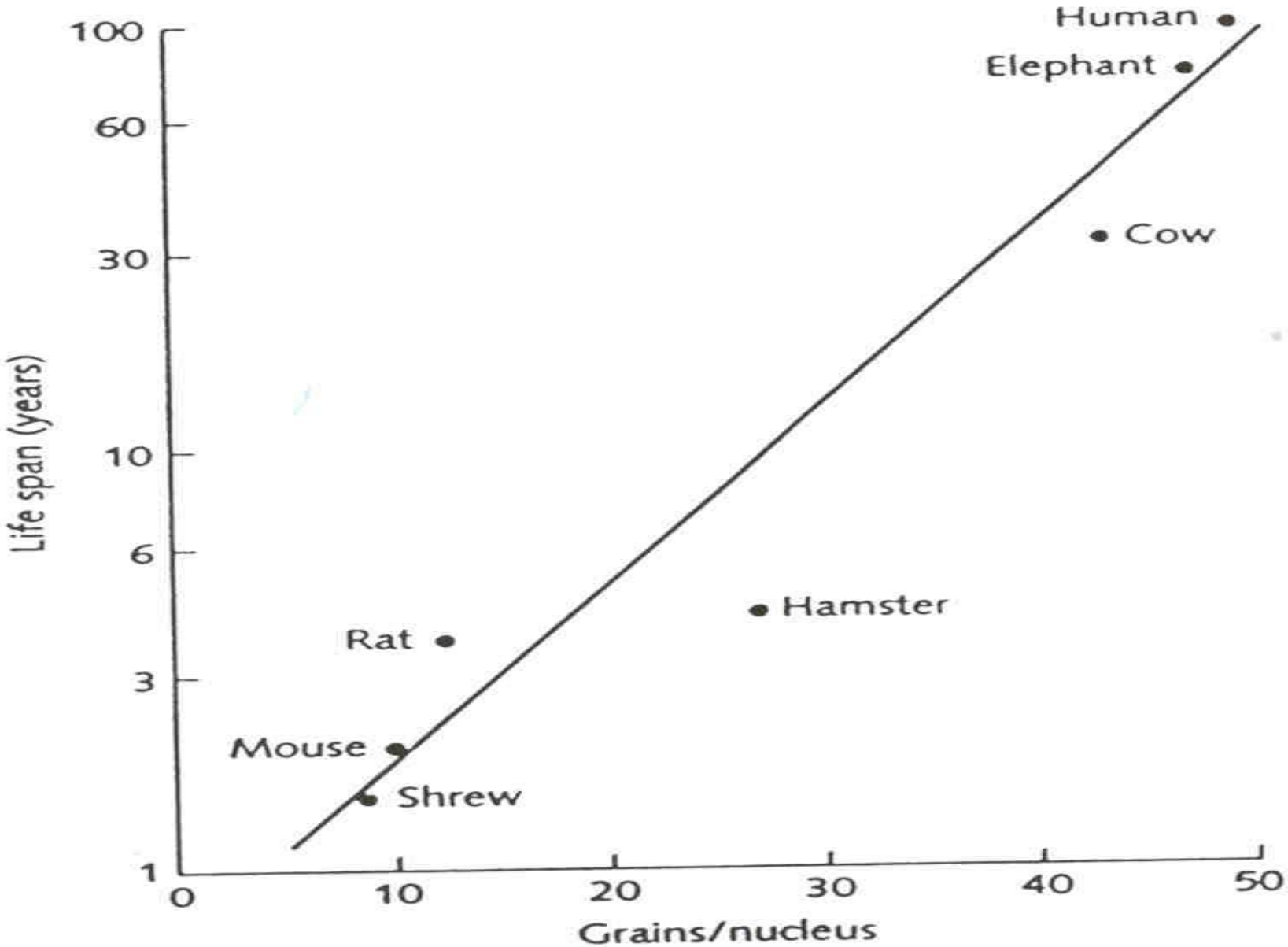



Mitochondria production of free radicals
Mitochondria dysfunction

- ***Extent of Genetic Damage***

- DNA damage occurs 36,000 to 160,000 times/day/cell
    - Most cells have DNA damage repair mechanisms
        - Relates to longevity

DNA Repair proteins



Protection against cell damage by free radicals

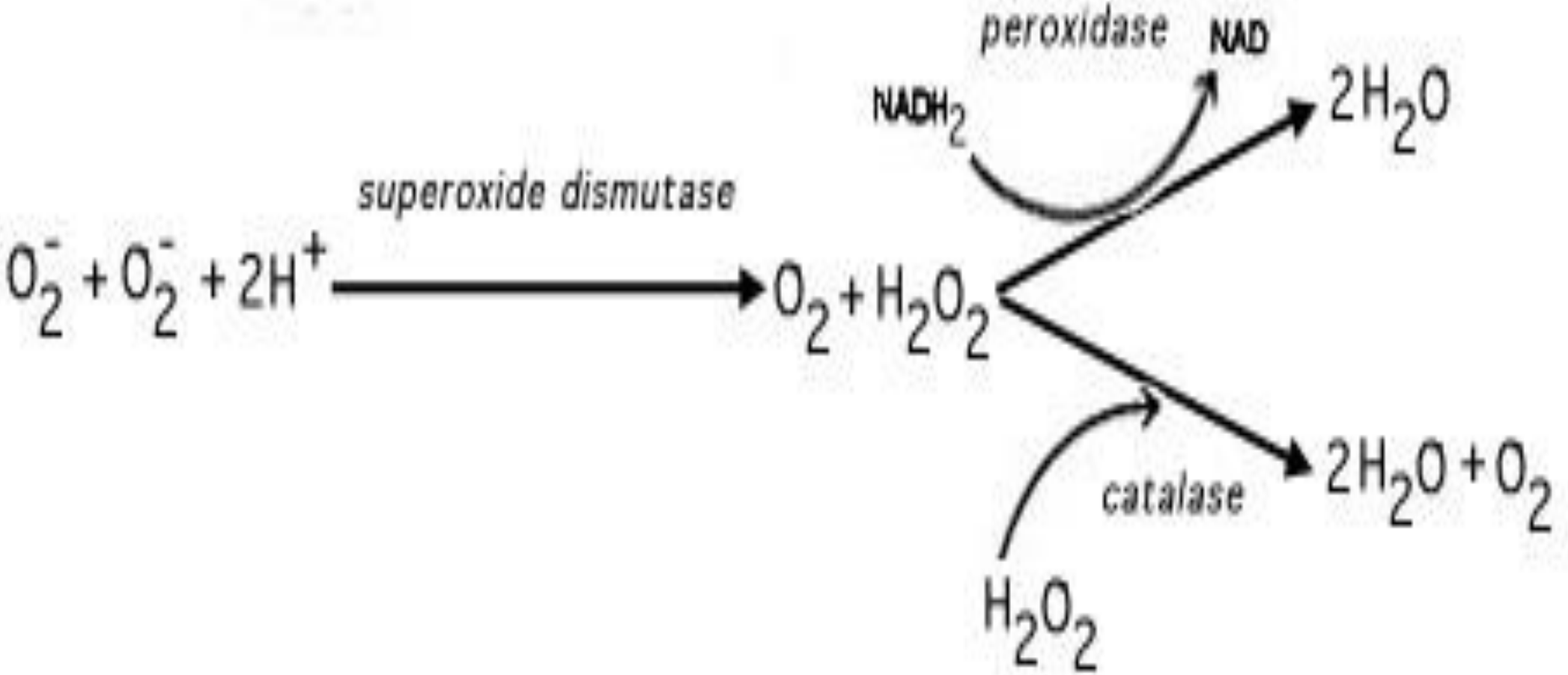
1) Enzymes (proteins) which alter structure of free radicals

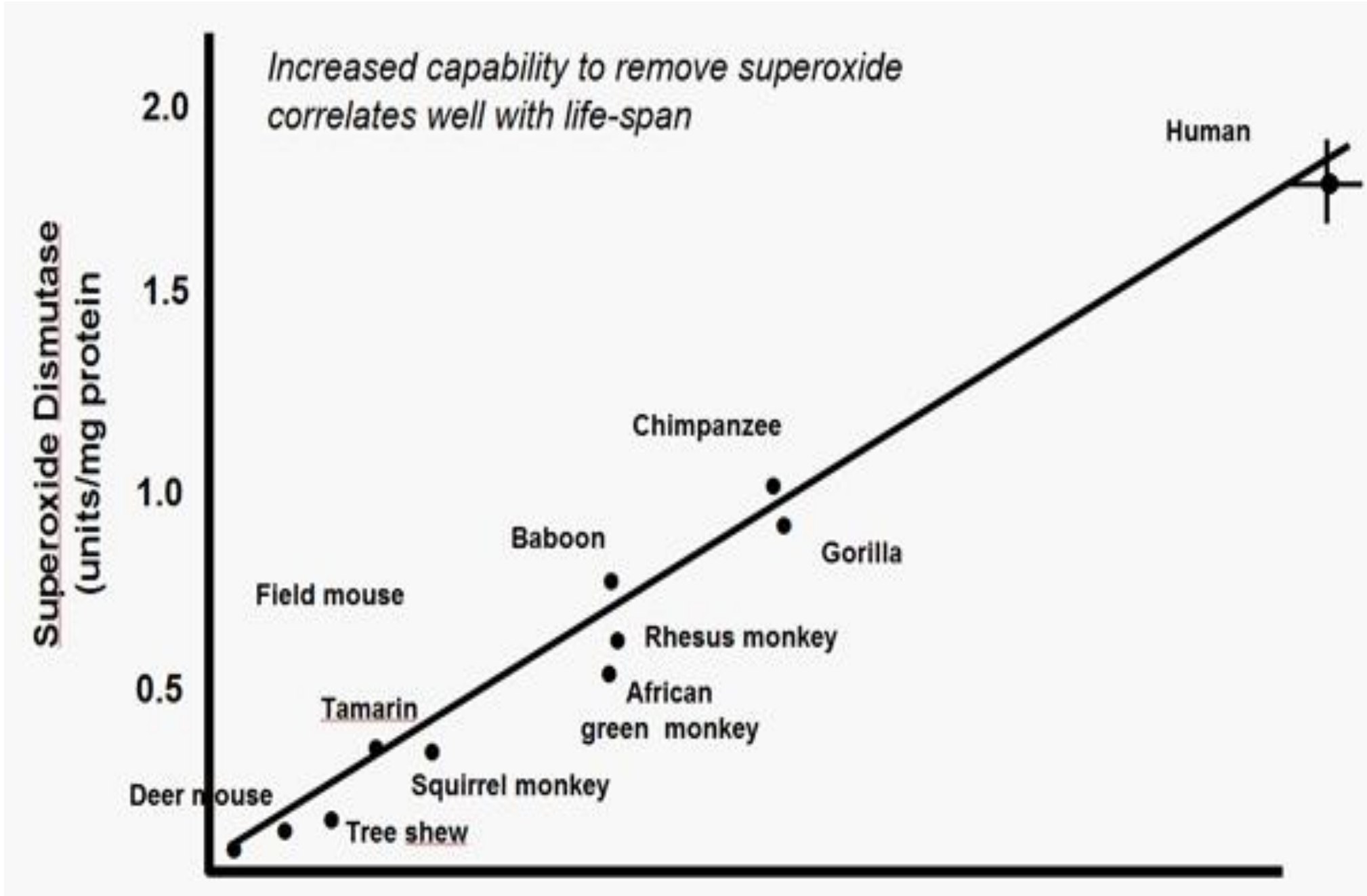
2) Antioxidant foods which donate an electron to a free radical

Longevity Assurance Genes

The family of *inherited* genes that code for enzymes that neutralize free radicals.

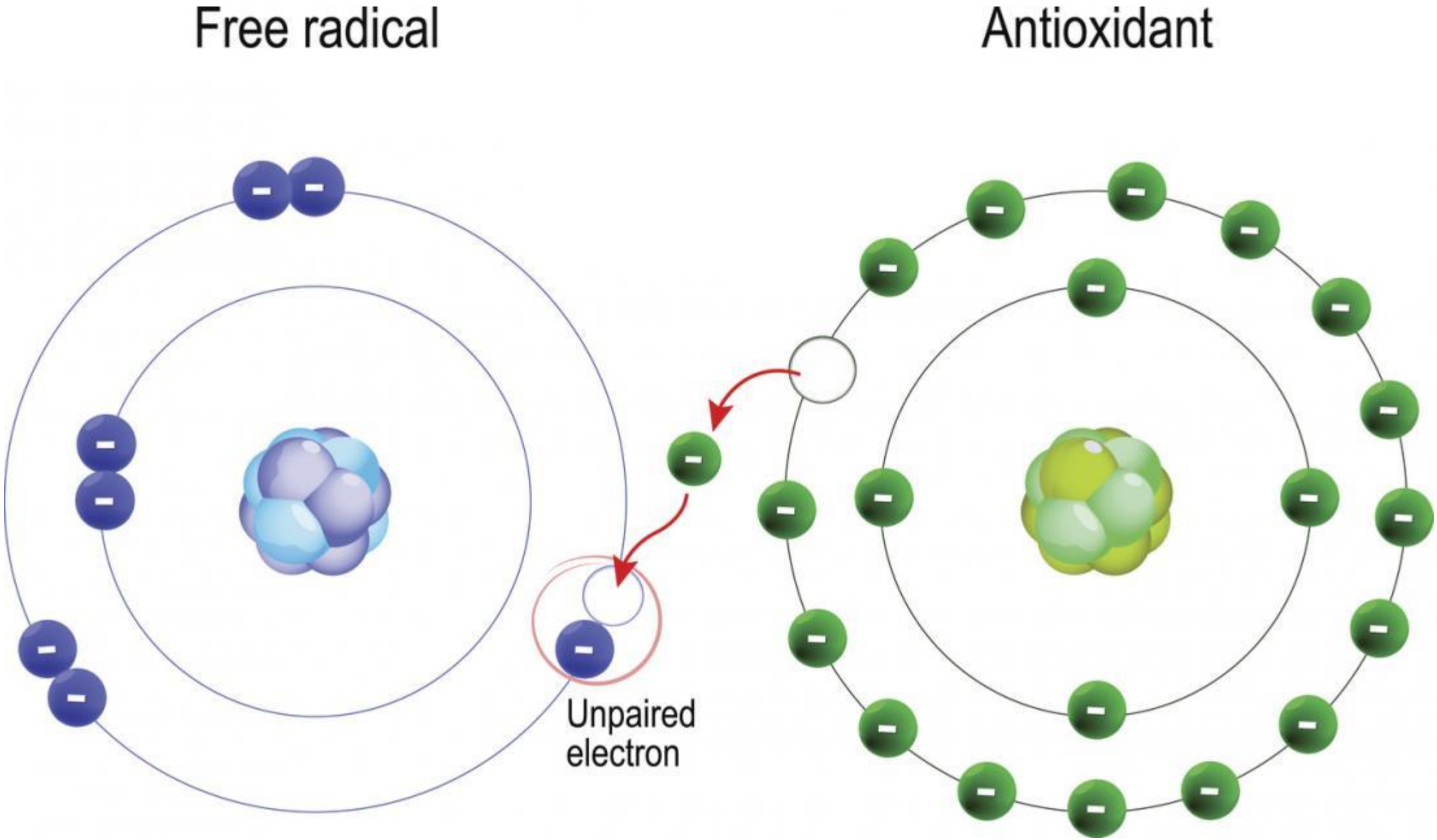
Cascade of enzymes that neutralize the superoxide molecule



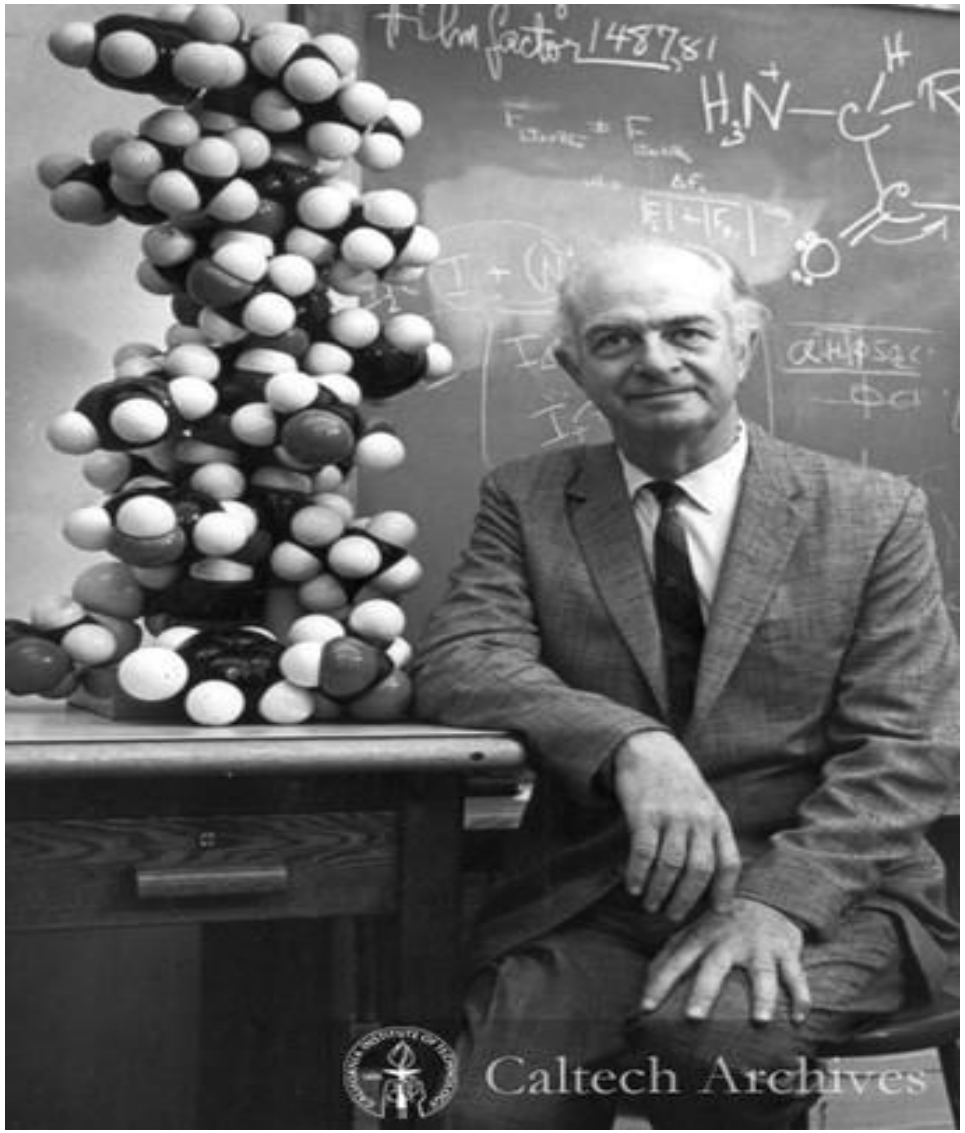

Increased capability to remove superoxide correlates well with life-span
Superoxide Dismutase (units/mg protein
2.0
1.5
1.0
0.5
Human
Chimpanzee
Gorilla
Baboon
Field mouse
Rhesus monkey
African green monkey
Tamarin
Squirrel monkey
Deer mouse
Tree shew

Antioxidants

- Substances such as Vit E & C, carotene, dark fruits and vegetables, and even caffeine and wine will *neutralize oxygen radicals by supplying the missing electron.*


Free radical
Antioxidant
Unpaired electron

The health benefits of vitamin C, Linus Pauling



Nobel Prize in chemistry, 1954; Nobel Peace Prize, 1962

TOP ANTIOXIDANT FOODS

	ORAC* UNITS PER 100 GRAMS
Dark Chocolate	**13,120**
Milk Chocolate	**6,740**
Prunes	5,770
Raisins	2,830
Blueberries	2,400
Blackberries	2,036
Kale	1,770
Strawberries	1,540
Spinach	1,260
Raspberries	1,220
Brussels sprouts	980
Plums	949
Alfalfa sprouts	930
Broccoli florets	890
Oranges	750
* Grapes, red	739
Red bell pepper	710
Cherries	670
Onion	450
Corn	400
Eggplant	390

Source: Data from U.S. Department of Agriculture and the *Journal of the American Chemical Society*.

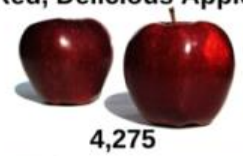
* ORAC (Oxygen Radical Absorbance Capacity) is a measure of the ability of foods to subdue harmful oxygen free radicals that can damage our bodies.

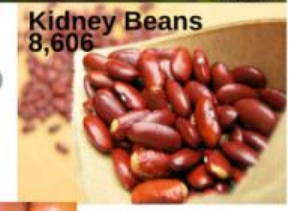
ORAC = oxygen radical absorptive capacity/100g

*Red wine 7,500

ANTIOXIDANT VALUES (ORAC) OF COMMON FOODS

www.lifeisbetteroiled.com





Guides to antioxidant foods

https://www.medicalnewstoday.com/articles/325873
https://www.webmd.com/food-recipes/features/10-super-foods
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2841576/

Areas of research into DNA damage associated with aging:

Steps in genetic expression

DNA surface molecules (epigenetics)

Telomere (caps on the end of chromosomes) damage

Genetic expression – activation of a gene to synthesis of a protein

Fundamental steps in genetic expression

Any and all steps subject to oxidative (free radical) damage.

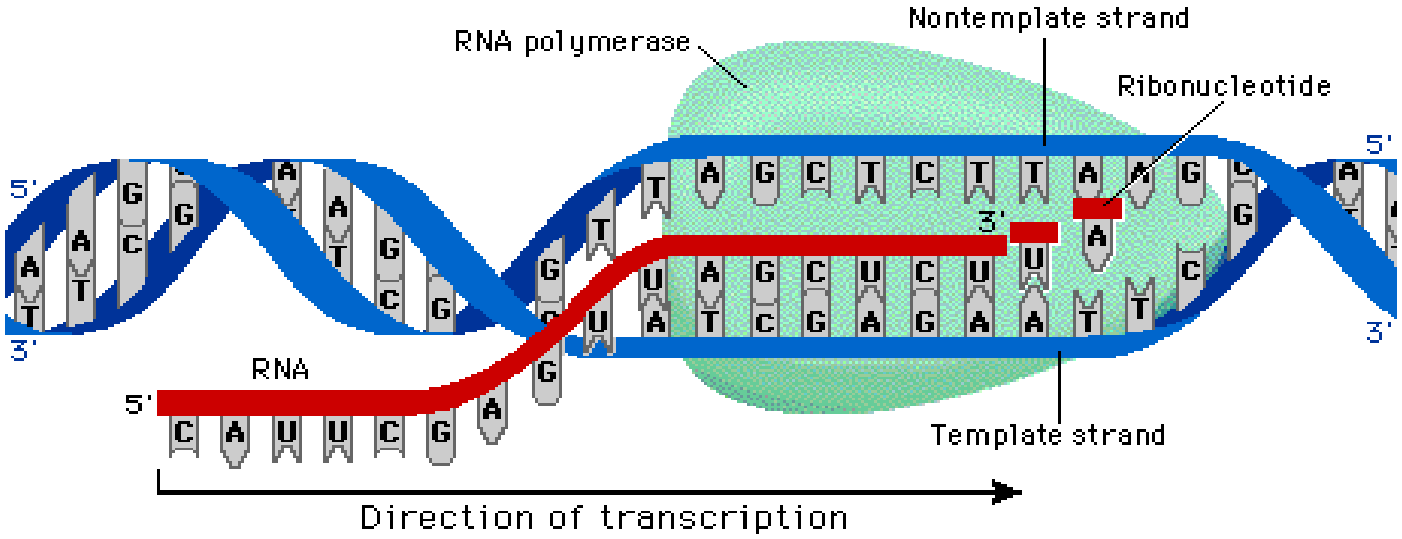
Transcription – occurs in cell nucleus
DNA to messenger RNA (mRNA)

Translation – occurs in cell cytoplasm
mRNA to amino acid sequence

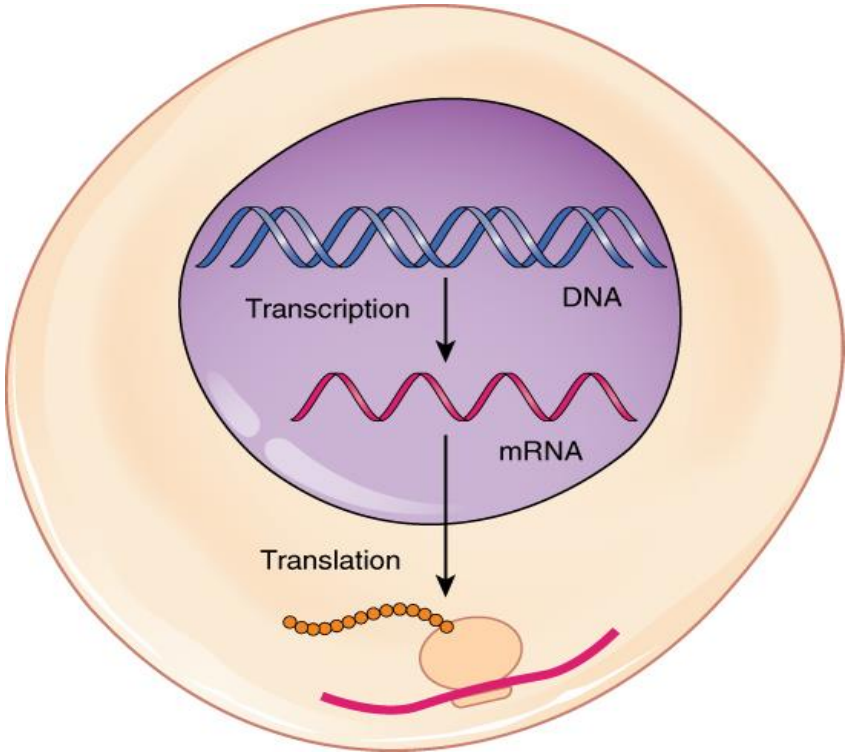
Post translation protein construction – occurs in cell cytoplasm
Amino acid sequence to final protein

Steps in genetic expression

- ***Transcription:*** A signal making its way into the cell nucleus triggers the unwinding of DNA on a chromosome at the site of the gene being expressed.
  - The unwound DNA (Deoxyribo Nucleic Acid) which contains the genetic code, makes a copy of itself in the form of a similar molecule called messenger Ribo Nucleic Acid (mRNA).



- ***Translation:*** The mRNA carrying the genetic code traverses from the nucleus into the cytoplasm.
- In the cytoplasm mRNA guides assembly of the sequence of amino acids that comprise the primary structure of the protein to be made.
- The language of DNA (sequence of nucleotides) is ***translated*** into the language of a protein (sequence of amino acids).



A relevant aside:

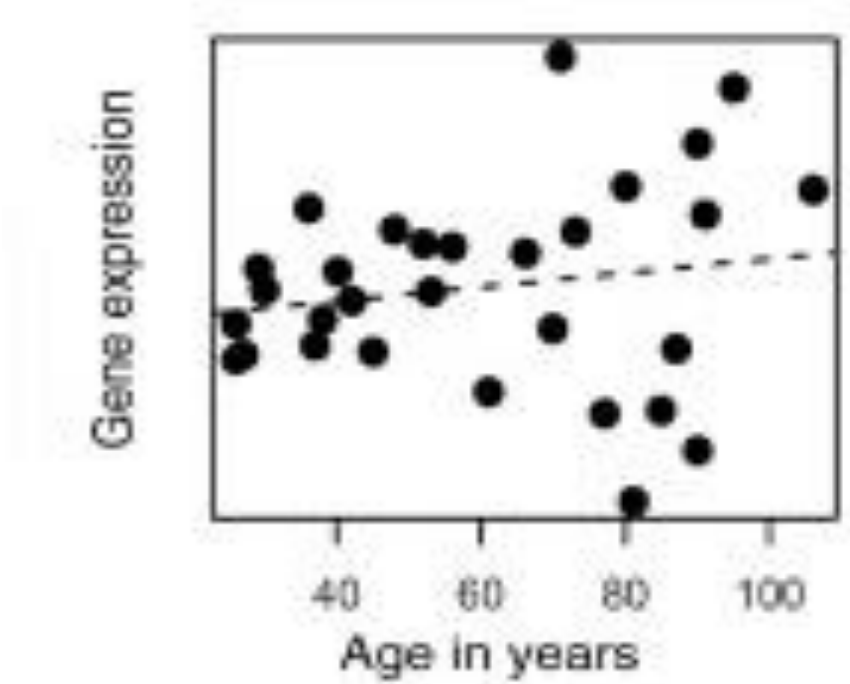
The Pfizer and Moderna vaccines contain the mRNA that makes the spike protein characteristic of the Corona virus.

Those spike proteins are seen as foreign by the immune system.

The immune system creates antibodies against the spike protein.

These antibodies will neutralize spike proteins on the real virus which destroys it.

Genetic expression becomes highly variable with age*.

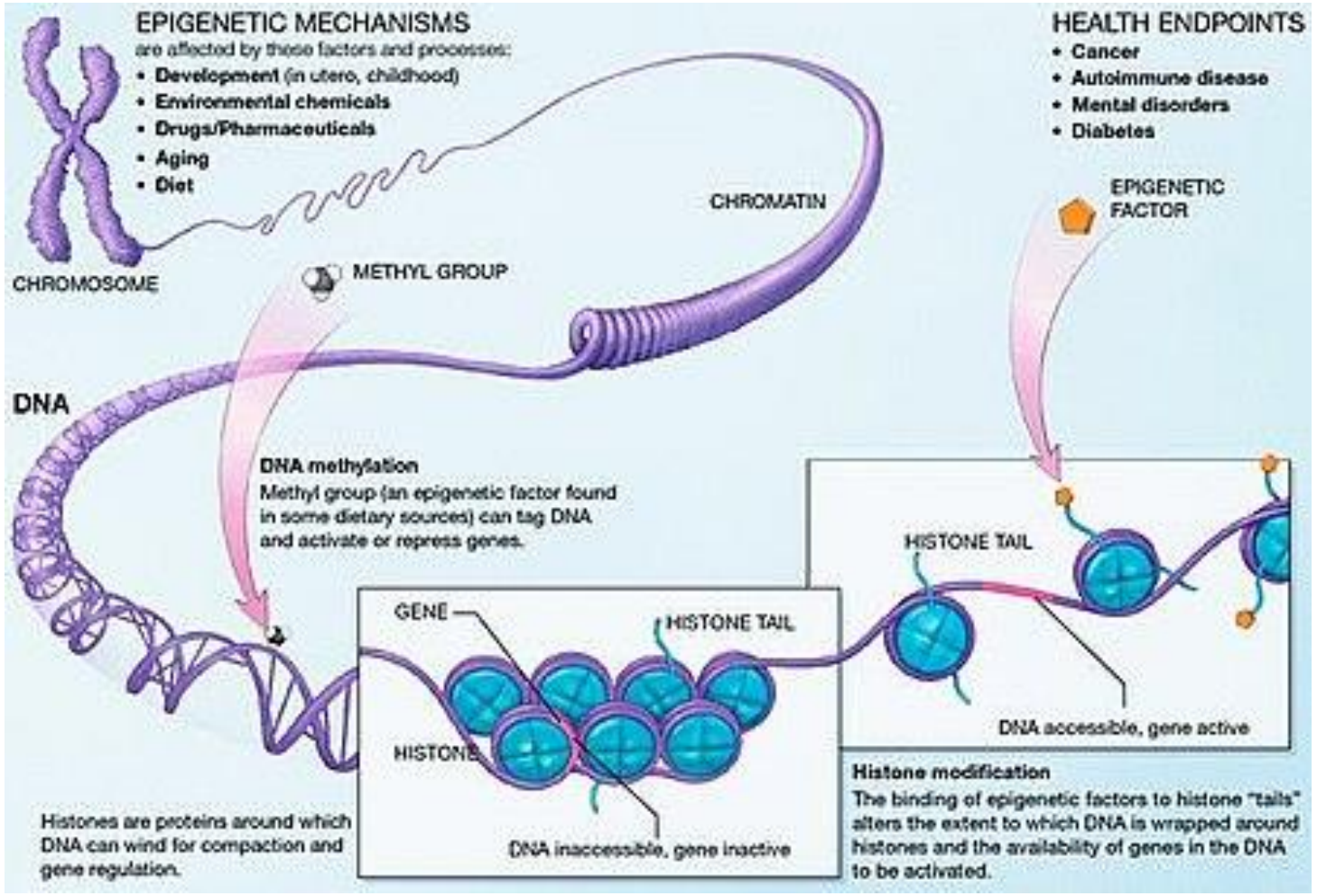


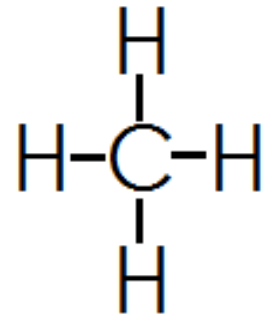
Can result in dysfunction of any protein component of a cell:

*Current Biology Vol 16, p R359, 2006

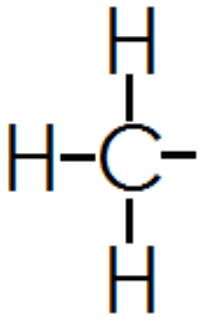
Epigenetic (surface) molecules on DNA initiate and control genetic expression

Absorb first hits of oxidative damage and other environmental factors*





methane



methyl group

* Mechanism by which environment can directly affect DNA

Diet

Seasonal affective disorder

Psychological state

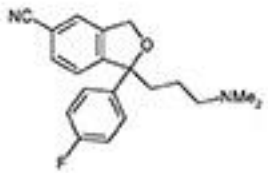
Diurnal/Seasonal correlations

Social Interactions

Disease exposure

Alternative medicine

Toxic Chemicals



Therapeutic Drugs

Drugs of Abuse

Microbiome

Exercise

Financial Status

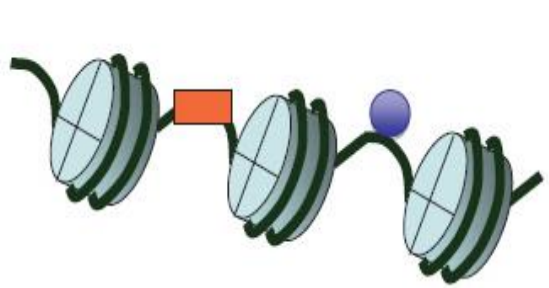
Conrad Waddington, British biologist coined the term epigenetics in 1942 (before structure of DNA was known) to refer to how genes might interact with the environment.

We now know that the environment does affect genes through the actions of epigenetic molecules.

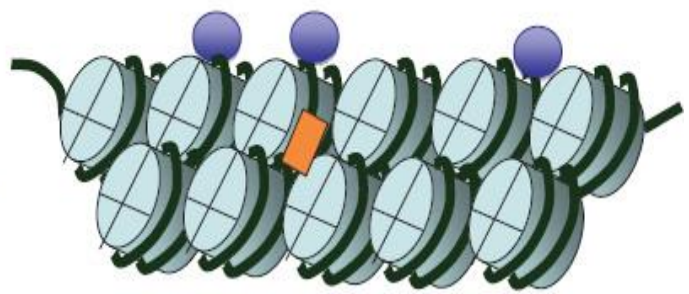
Epigenetic modification alters which genes are on or off

ON

OFF

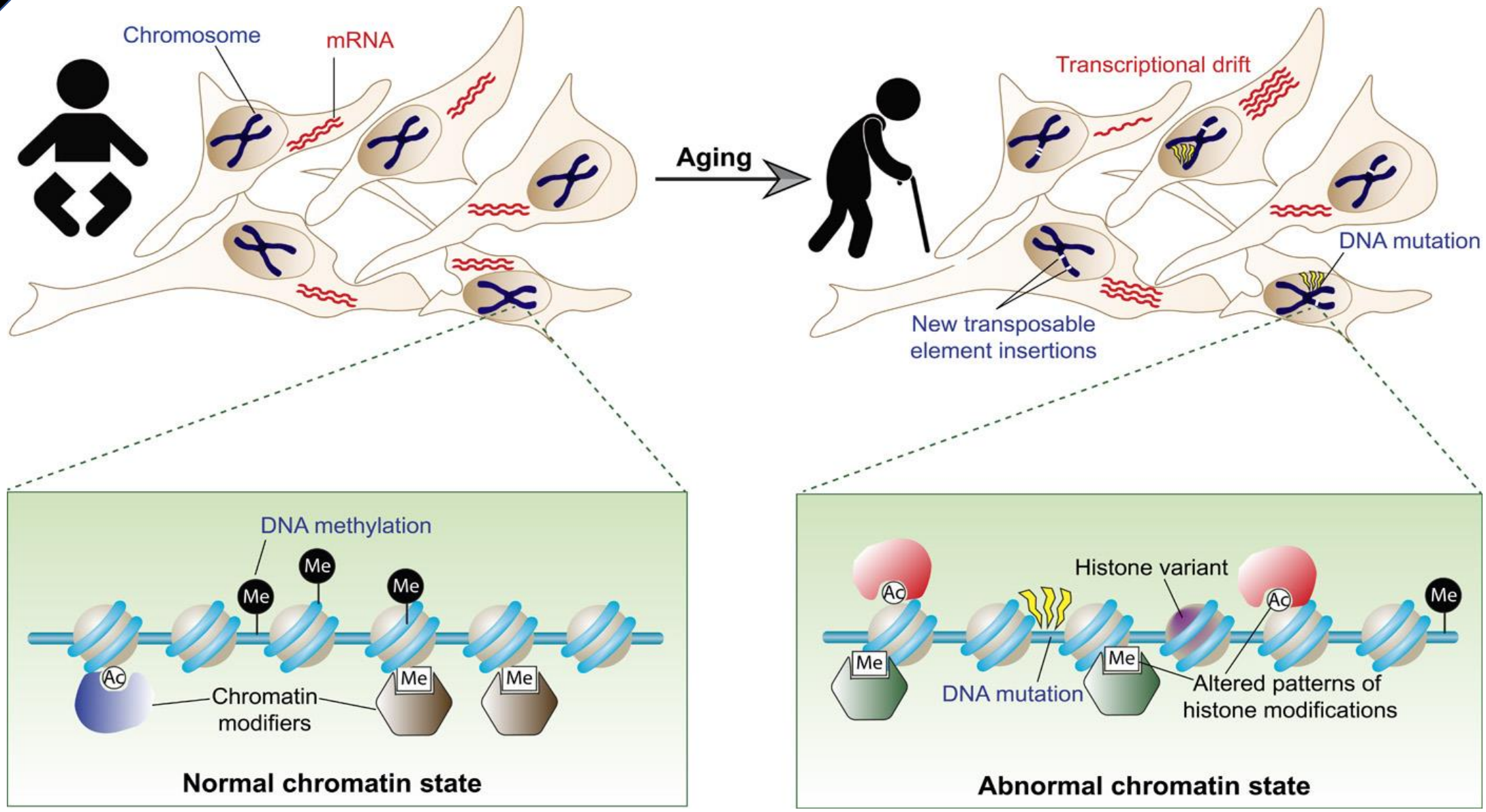


vs.



DNA methylation and aging:

↓ in degree of DNA methylation; ↑ in variability of methyl functions

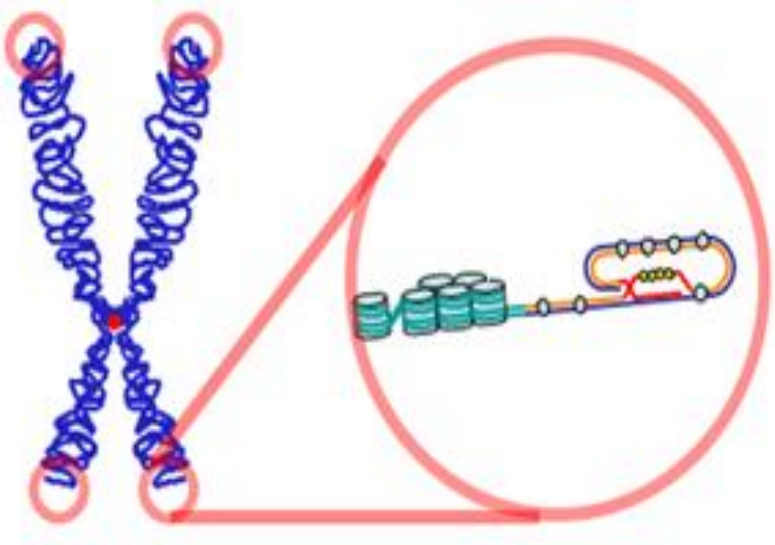


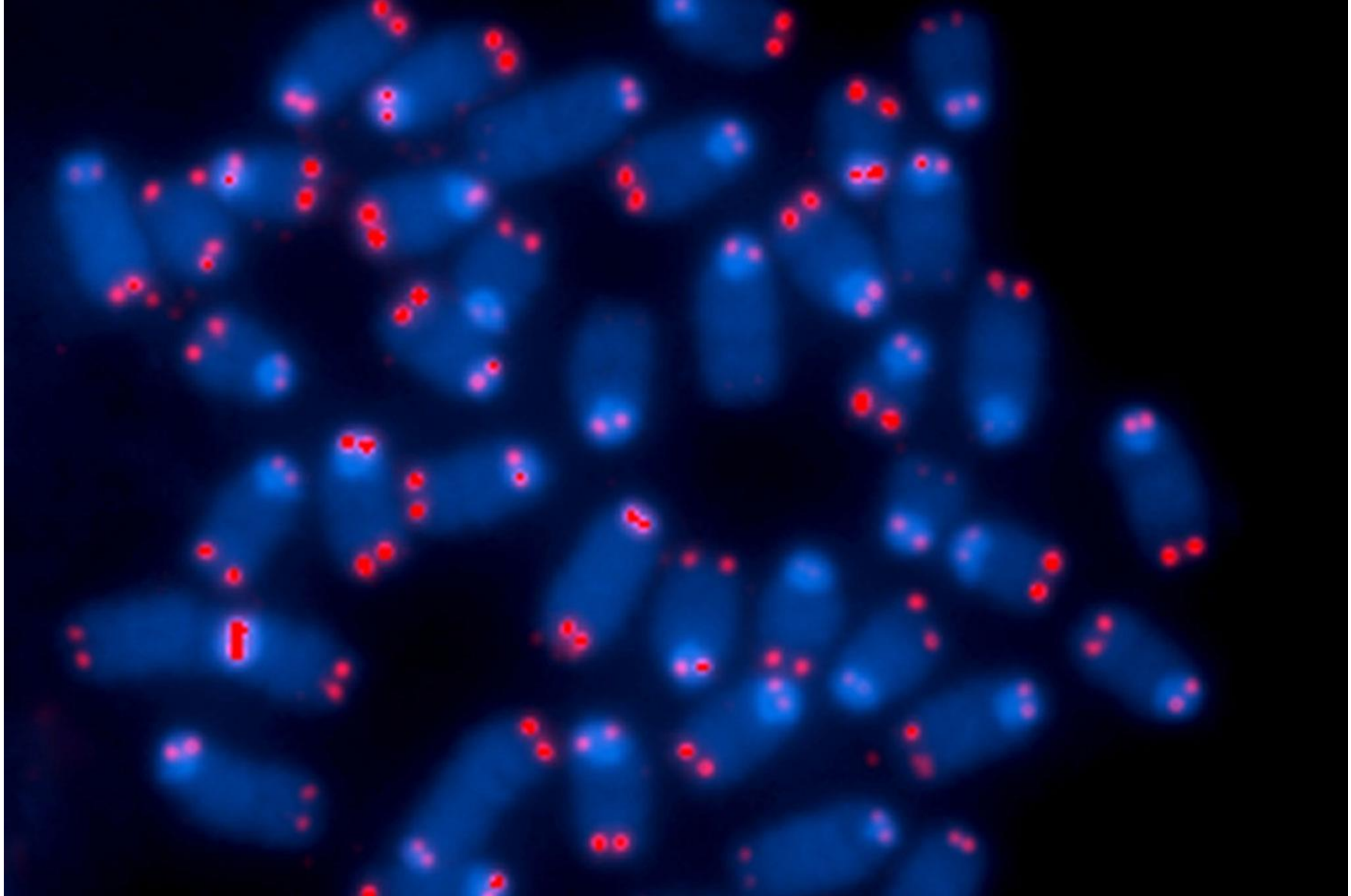
Steve Horvath, UCLA biostatics developed DNA methylation analysis as a predictor of age: An epigenetic clock, 2013

Telomeres (telos = end; meros = part):

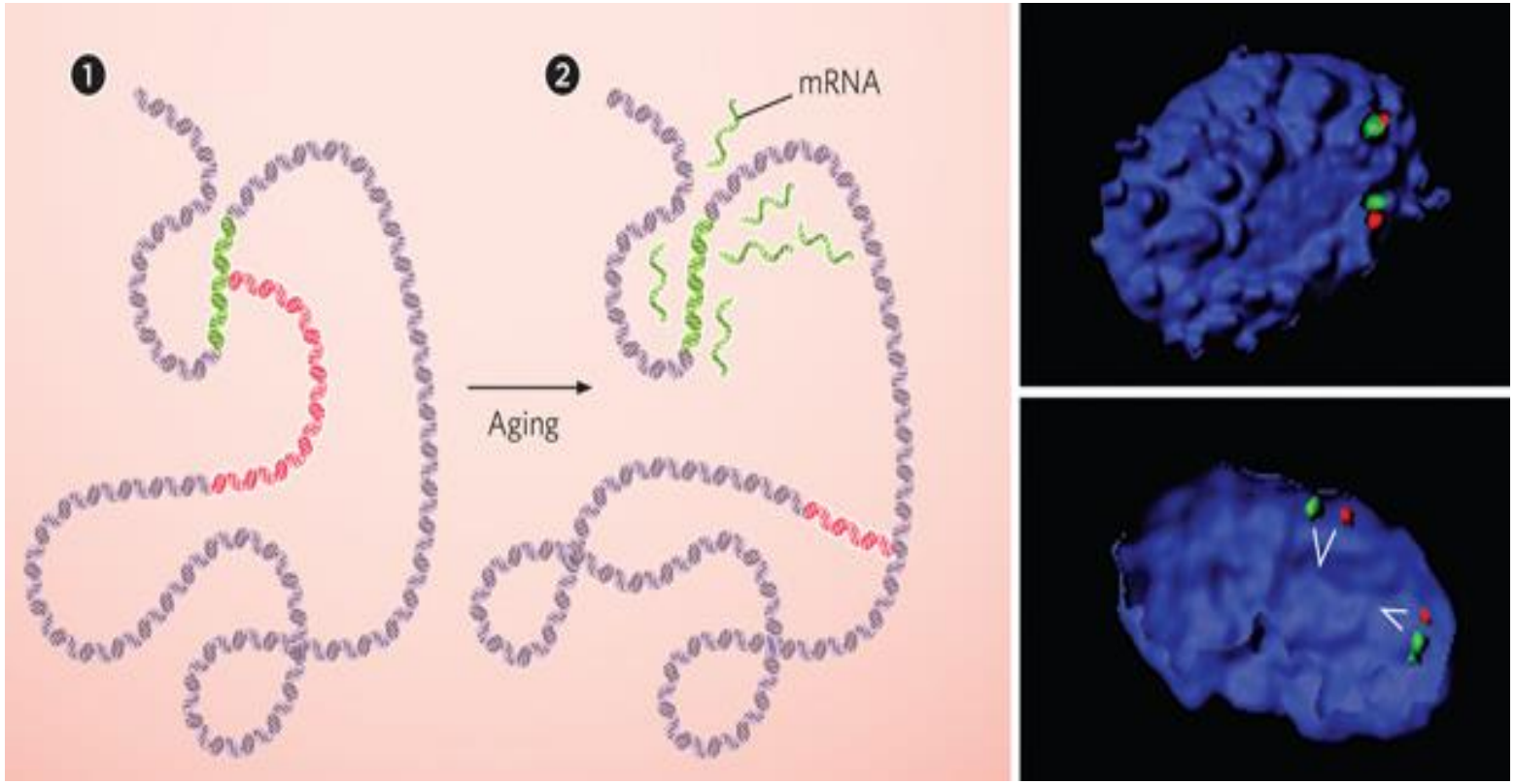
Repeating sequences of the base combination TTAGGG placed at the ends of a chromosome.

The role of telomeres is to keep the chromosomes from bonding to each other.





Telomeres may play a role in regulating genes



Barbara McClintock, American botanist hypothesized end elements on chromosomes that prevented them from “sticking” together (1933)

1983 Nobel Prize for her work on genetic control elements

Lenard Hayflick, American anatomist discovered that dividing cells, such as skin and GI, divide on average 52 times (range 40-60) before division ceases (Stanford Univ. circa 1961).

Later shown to be due to Telomeres reaching a minimal number of replications.

Telomeres and Aging

There are about 2,500 repeats of a telomere sequences at birth.

Every time a cell duplicates one or more sequences split off.

Some, but not all, are reconstructed by the enzyme telomerase.

By old age the average duplicating cell is down to about a 900 sequences.

Probably due in part to reduced telomerase.

The fewer the sequences, the more susceptible to damage.

Genetic Factors of Aging Not Related to DNA Damage

• Direct Genetic Programing:

- Holds that biological aging results from *direct* expression of a purposeful sequence of events written into the genome.
  - Arguments for and against:
  - ***For:*** Darwin felt that aging beyond reproductive years evolved to enhance survival of younger reproducing organisms. *(Really! Since when has anyone under 30 listened to anyone over 60?)*
  - ***Against:*** Others felt that organisms in the wild did not live long enough past reproductive years for aging gene to have evolved.

Genes that indirectly affect aging by extending lifespan
(Darwin may have been right after all)

CETP = cholesterol transfer protein

Sofiya Milman, American endocrinologist:
Discovered CETP gene (circa 2014)

CETP gene expresses CEPT which transfers cholesterol to high density lipoproteins (HDL).
HDL = the “good” cholesterol.
Removes cholesterol from blood vessels
Reduces atherosclerosis
Extends lifespan

Aging Resulting from Delayed Genetic Factors

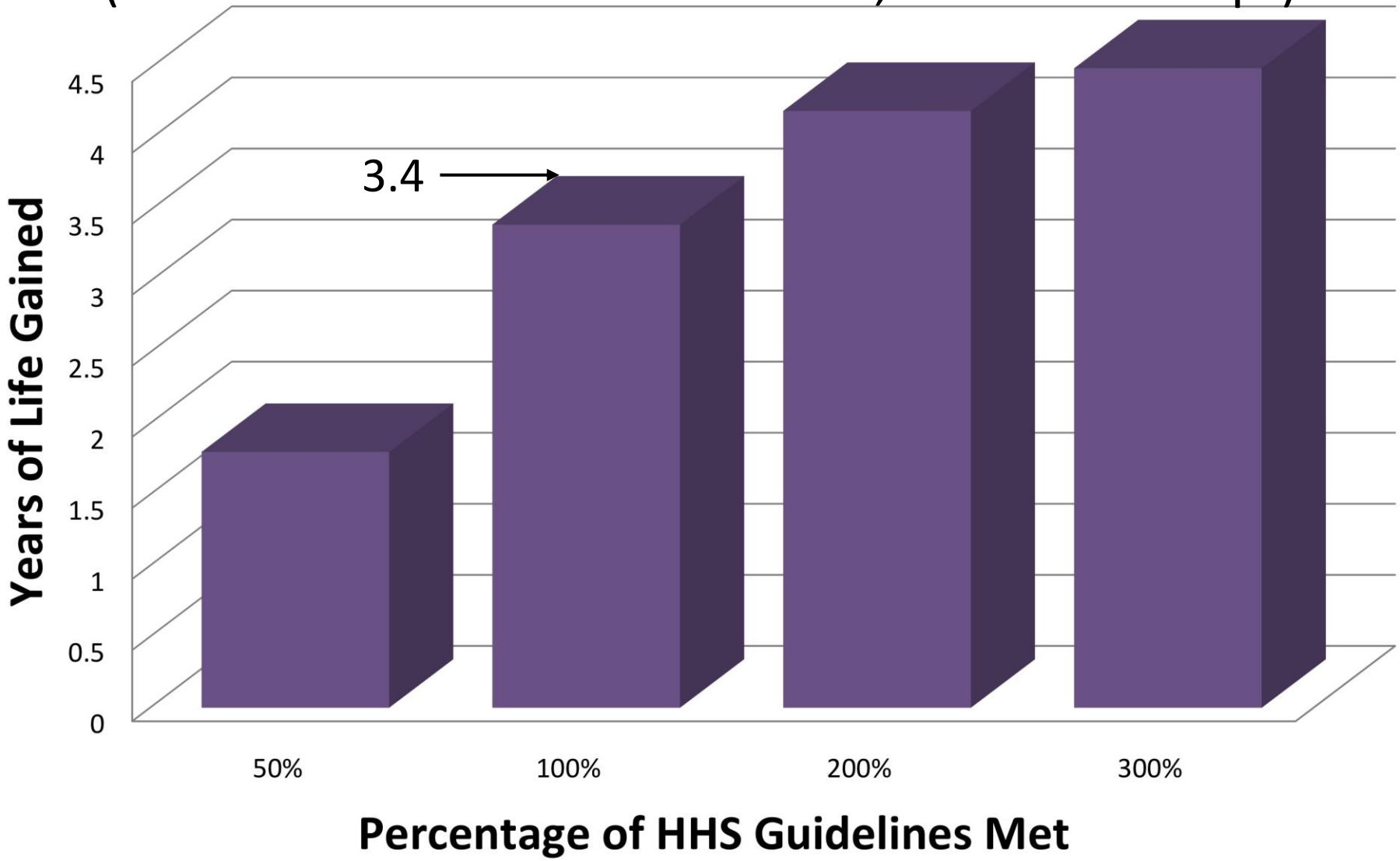
- The tenet of this notion is that aging is an indirect consequence of genes whose detrimental effects are not manifested until later in life.
  - Genes that lead to ill health later in life (e.g., Alzheimer's disease) tend not to be selected out, leaving them to remain hidden in the genome.
  - Genes that have a beneficial effect early in life but cause harmful effects later in life. Known as ***antagonistic pleitrophy.***
    - Testosterone: reproduction in youth; prostate cancer in aging

The age retarding effect of exercise: aka, the Ponce de Leon effect

Juan Ponce de Leon, 1474-1521

Life Expectancy Gains from Physical Activity

(HHS = Health & Human Services; aka Health Dept)



HHS Exercise Guidelines

2.5 hr moderate ex per wk (21 min per day)*

Walk
Slow jog
Bike (stationary is just fine)
Swimming
Racket sports

* Within age related exercise HR zone

Age related HR zone (American Heart Association)

Exercise at 50-85% of maximal heart rate (MHR)

MHR = (220 – age in years)

Age (yrs)	MHR (beats/min)
40	180
60	160
80	140

Ponce's math: If I exercise will I live longer or will it just seem like it?

Recommended exercise level for a healthy life: 2.5 hr/wk X 52 wk/yr = 130 hr/yr

Beginning exercise at above level at age 40 will increase life expectancy by 3.4 yr

Present live expectancy, 78 years

Life expectancy for exerciser, 78 + 3.4 = 81.4 yr

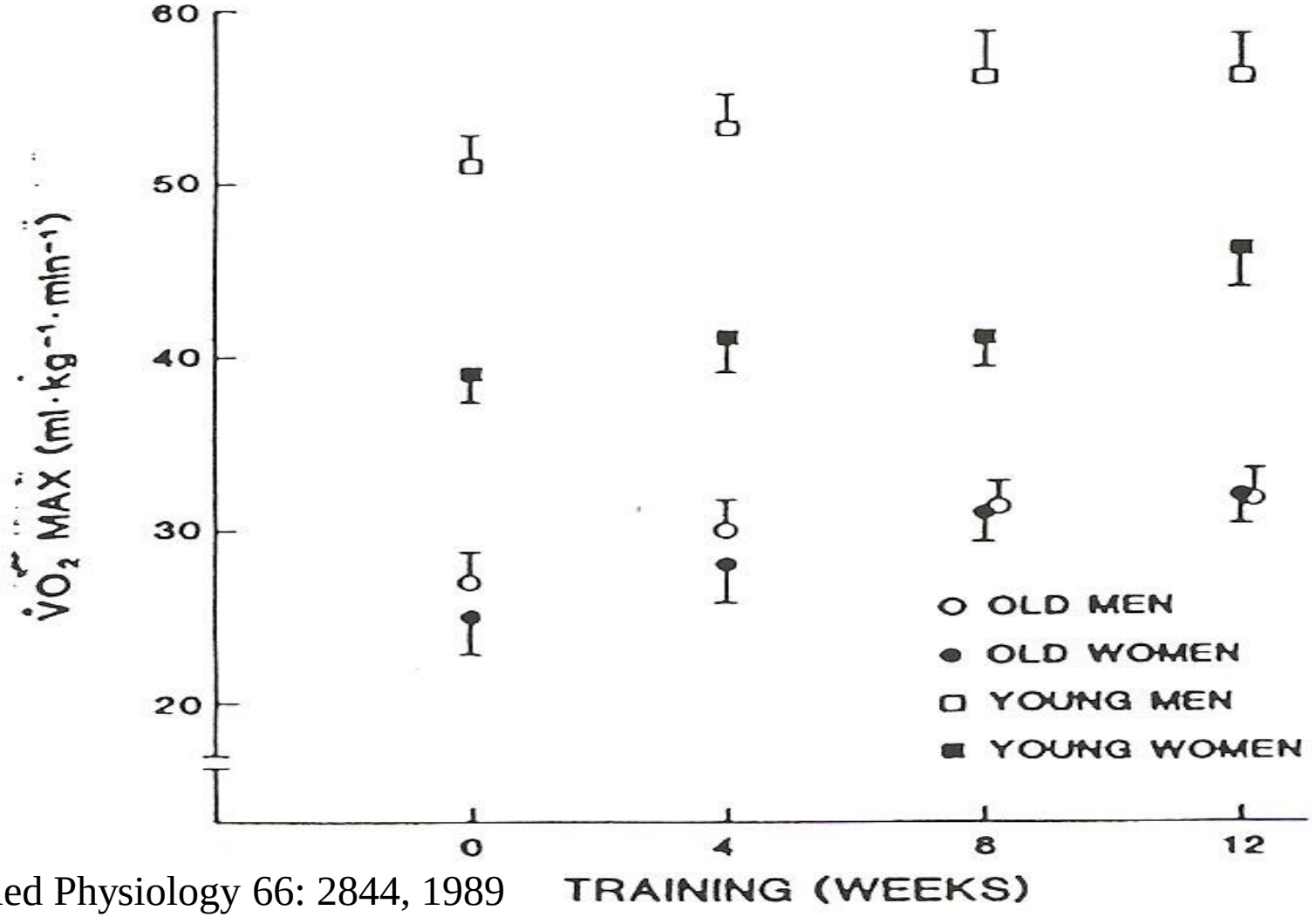
Begin exercise at age 40 (81.4 – 40 = 41.4 yr of exercise)

41.4 yr X 130 hr/yr = 5,382 hr: 5,382 hr/8,760 hr/yr = 0.614 yr

0.614 years of exercise will get you 3.4 years of additional life!!

Effects of exercise conditioning on maximal oxygen consumption - an indicator of physical work capacity – in 65 yr and 25 yr men & women

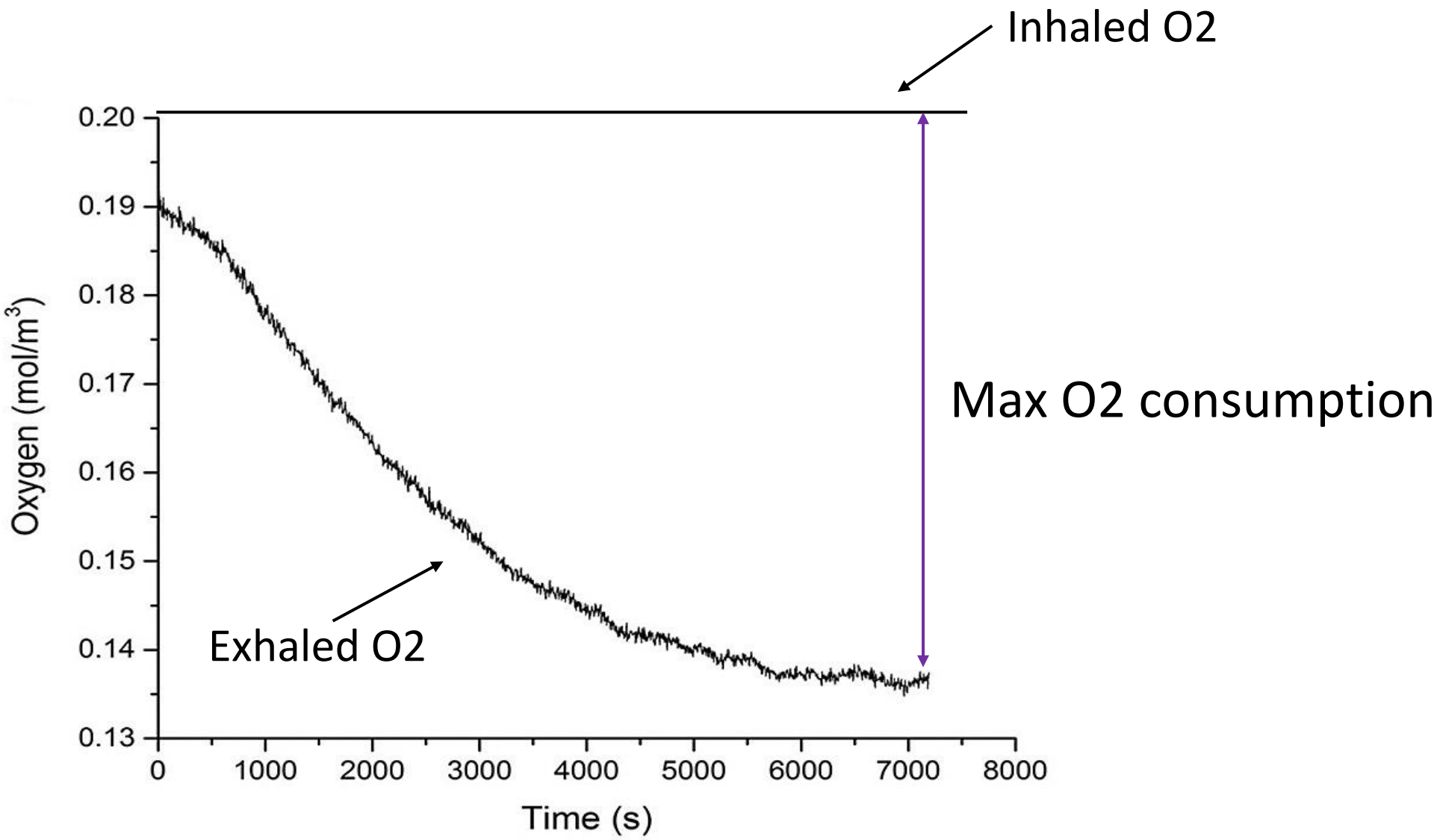
Max O2 consumption (ml O2/Kg body wt/min)



Journal of Applied Physiology 66: 2844, 1989


ATHLETS

O2 values during max O2 consumption test



Increased extraction of oxygen by muscle cells

muscle oxygen uptake (ml O_2/gram tissue/hour)

age	before ex conditioning	after ex conditioning
24	1.77	2.26
65	1.05	2.28

Journal of Applied Physiology 66: 2844, 1989

Increase in muscle strength with resistance training

(Journal of Applied Physiology 64: 1038, 1988)

60 to 72 yr old men

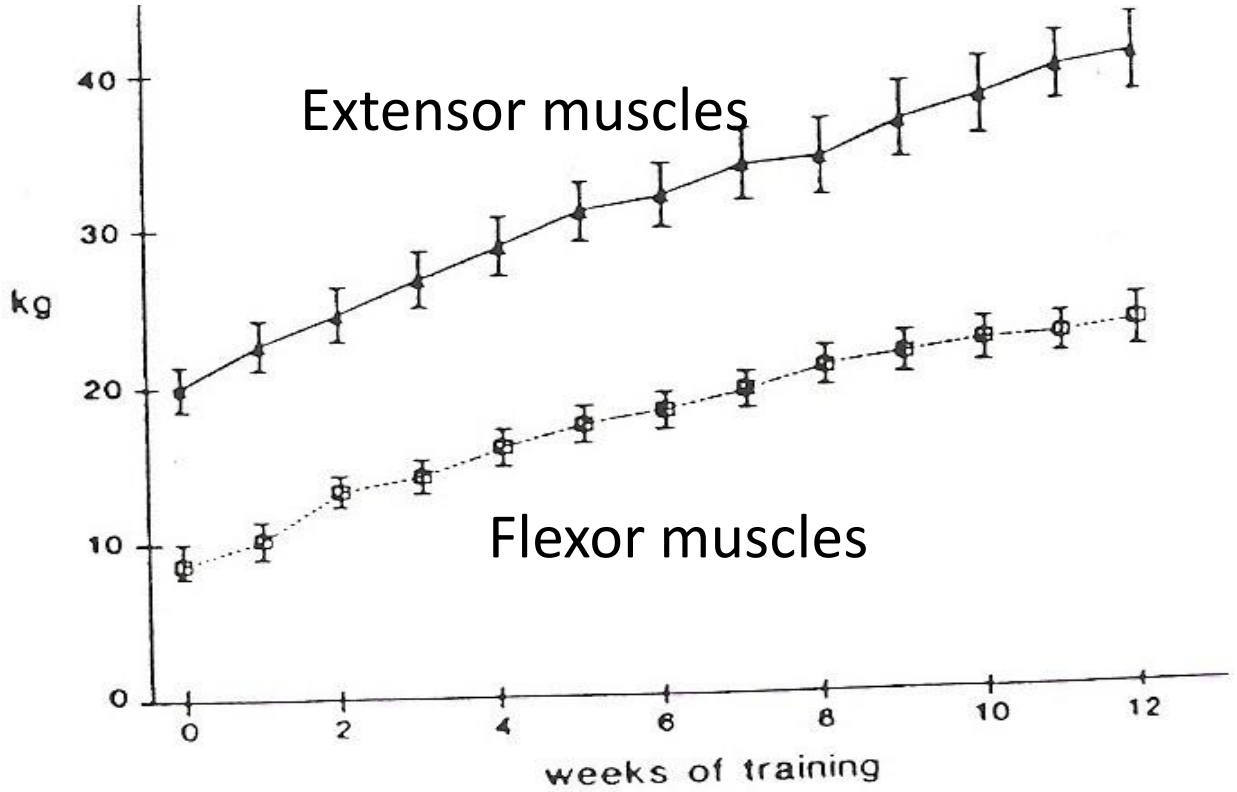


FIG. 2. Weekly measurements of dynamic muscle strength (1-repetition maximum) of left knee extensors (-▲-) and flexors (-□-). Results are means ± SE.

Reduces age-related loss of muscle mass

increase in basal (resting) metabolic rate

- Mechanism by which exercise conditioning helps to control body weight
  - Increase in number, size and efficiency of mitochondria in muscle cells
    - Most effective with aerobic exercise (eg, walking, biking, swimming)
    - Increase production and use of ATP by muscle cells
      - (Robert H. Lustig "*Fat Chance",* 2013, Ch 13

Reduction in insulin resistance, the cause of Type II diabetes

(*Handbook of Physiology: Aging*, 1995, chapter 24, p 657)

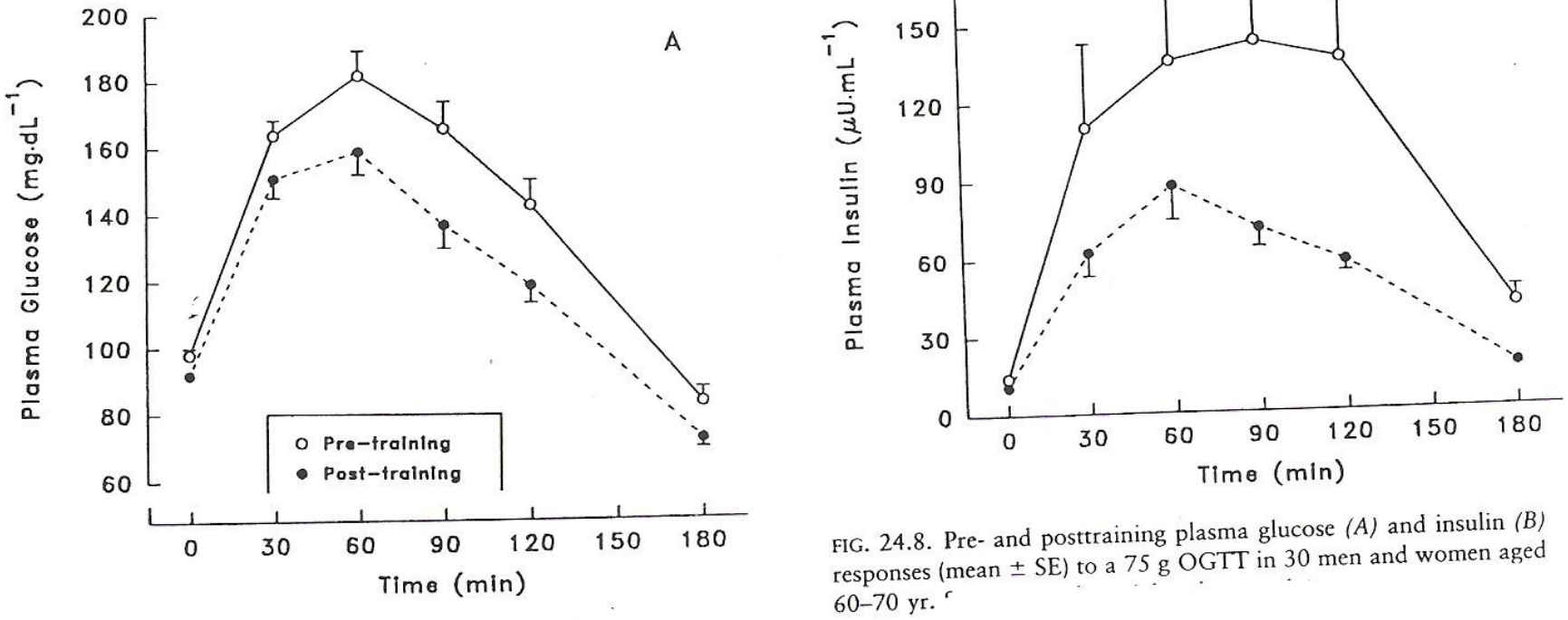


FIG. 24.8. Pre- and posttraining plasma glucose *(A)* and insulin *(B)* responses (mean ± SE) to a 75 g OGTT in 30 men and women aged 60–70 yr.

Increase mineralization (calcium) of bone

(International Journal of Sports Medicine 11: 208, 1990)

Subject group (postmenopausal women)	Cortical (long) bone mineral content (grams/cm bone)
Low level of walking*	0.701
High level of walking*	0.813

*Load bearing exercises, like walking, stimulate bone cells to take up and deposit calcium.

Is there a downside to all this exercise stuff?

Sort of: During exercise the production of ATP via the consumption of oxygen produces damaging oxidative free-radicals.

However: Conditioning, 22 minutes of exercise per day, will reduce daily (24 hr) oxidative stress.

Thought to be due to a more efficient use of oxygen to produce ATP

Med. Sci. in Sports and Exercise, vol 42, pp 1448-1453, 2010

Postmenopausal sedentary women (n=173, age 50-75 yr) randomly divided into two groups.

Aerobic exercise group: stretching followed by aerobic exercise

Intensity of 60% to 75% of maximal heart rate

Control group: stretching only

At the end of one year urine samples were measured for F2-isoprostane, (a marker of oxidative stress)

Exercise group showed a 6.2% decrease in F2-isoprostane

Control group showed a 3.3% increase in F2-isoprostane

Hypothetical coupling of exercise to reduced aging

Exercise conditioning (2.5 hr aerobic ex/week)

Promotes expression of telomerase, a protein that replaces damaged telomeres with new ones.

Inhibits telomere reduction during chromosome activity

Enhance expression of anti-oxidant and DNA protective enzymes

Reduces oxidative stress

Reduces biological aging

National Institute of Aging exercises

https://www.nia.nih.gov/health/exercise-physical-activity

Jackie Sorenson dance exercises

https://www.jackis.com/dance