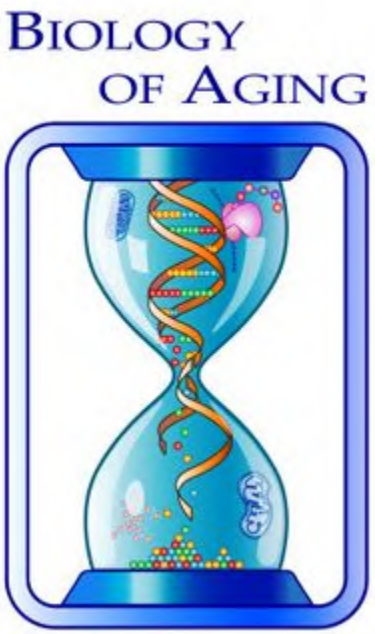
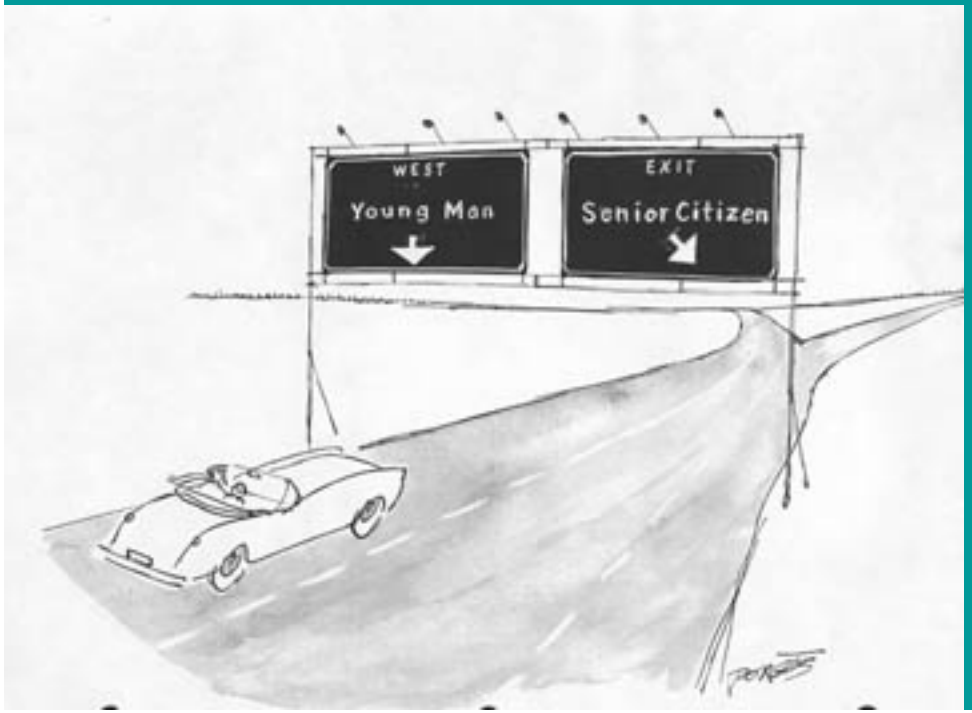
The mechanisms of the aging.

The biological age.

The physiological and pathological aging.






Stay connected to your alumni. Forever.

The Real Diana


1971


1980


1985


1989


1992


1997

DIANA at 46?

AUGUST 13, 2007

People

Photo Illustration by D'LYNN WALDRON

To read more about Diana's extraordinary life, order your copy of ***DIANA: An Amazing Life*** at **PEOPLE.COM/DIANABOOK.**

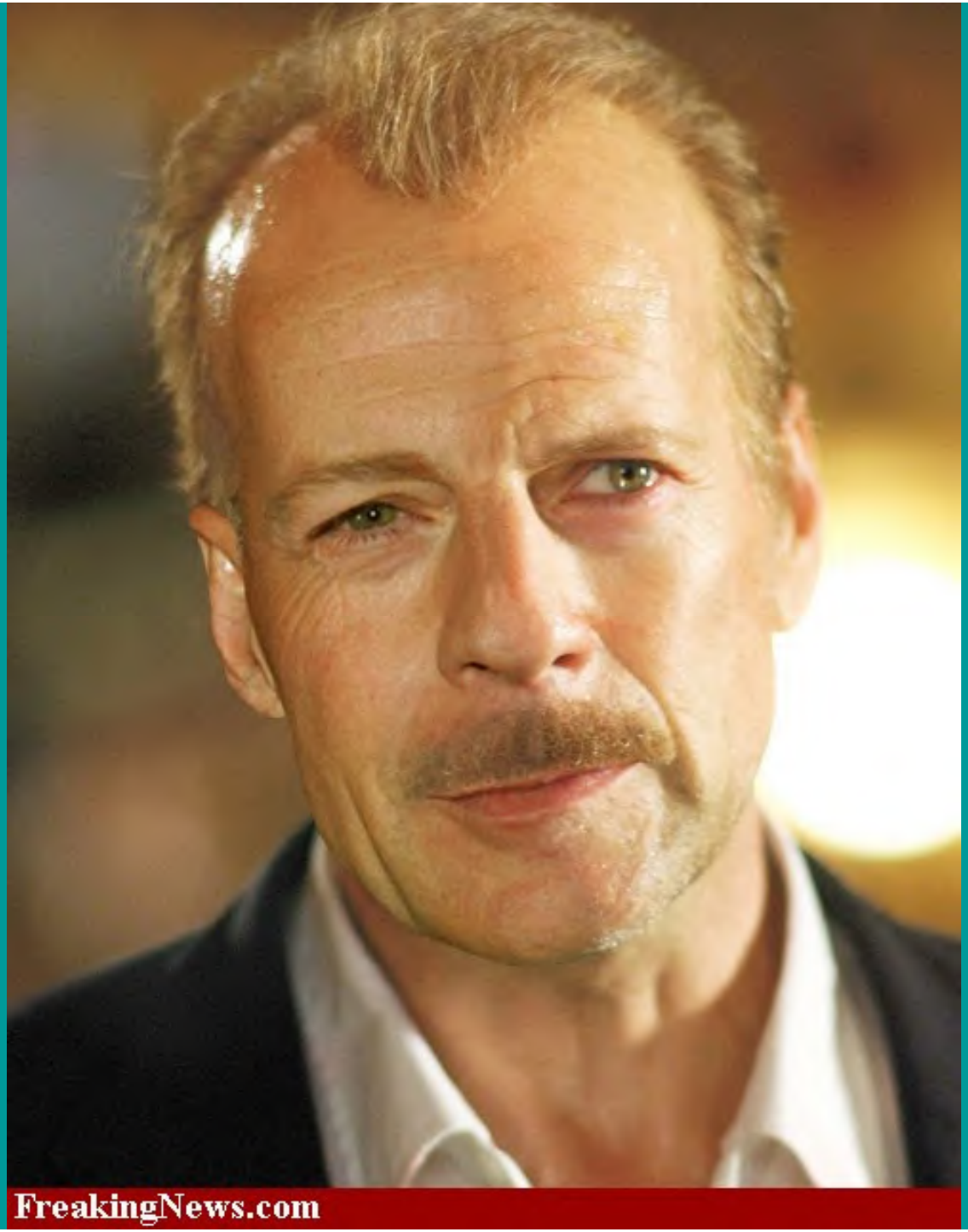

FreakingNews.com

Figure 8. Population aged 60 or over: world and development regions, 1950-2050

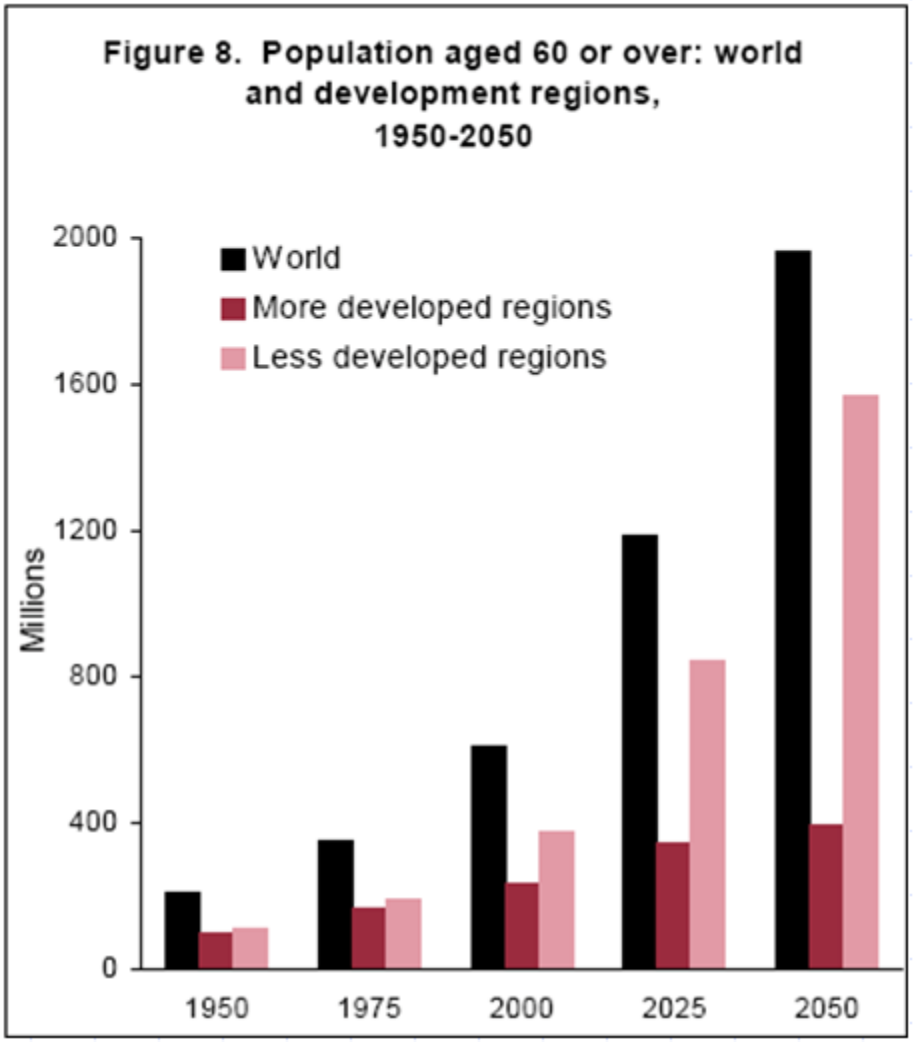
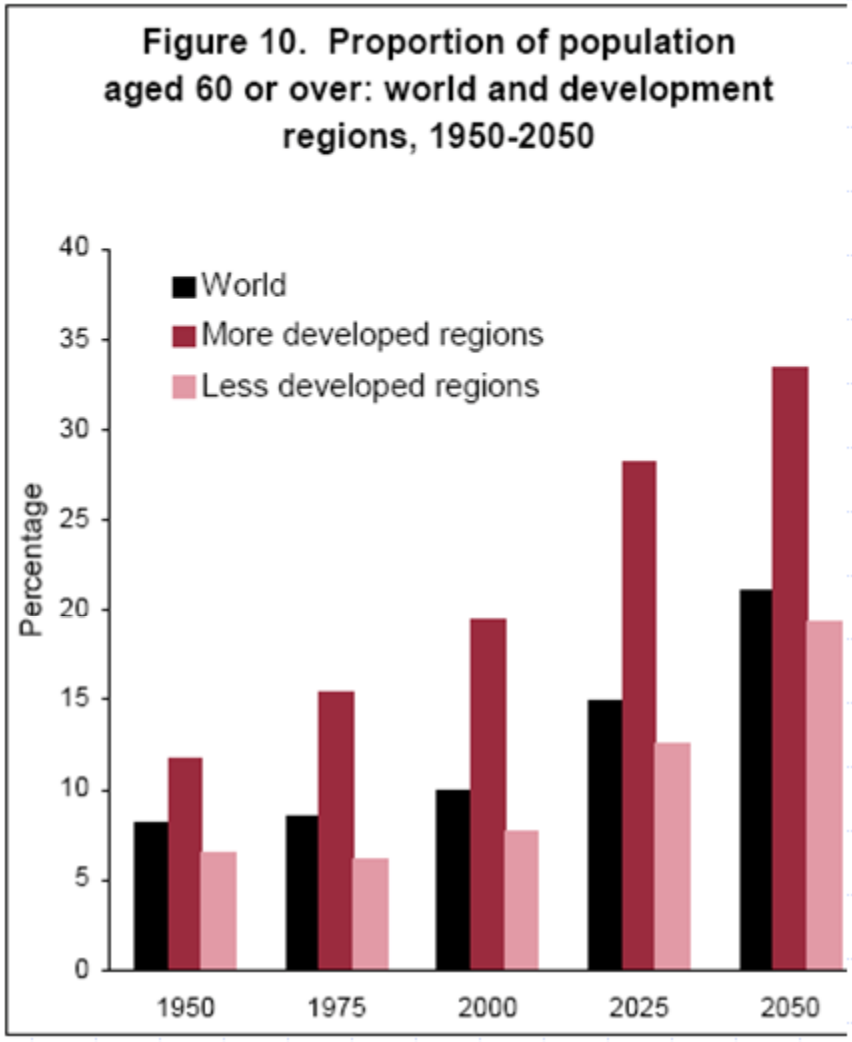


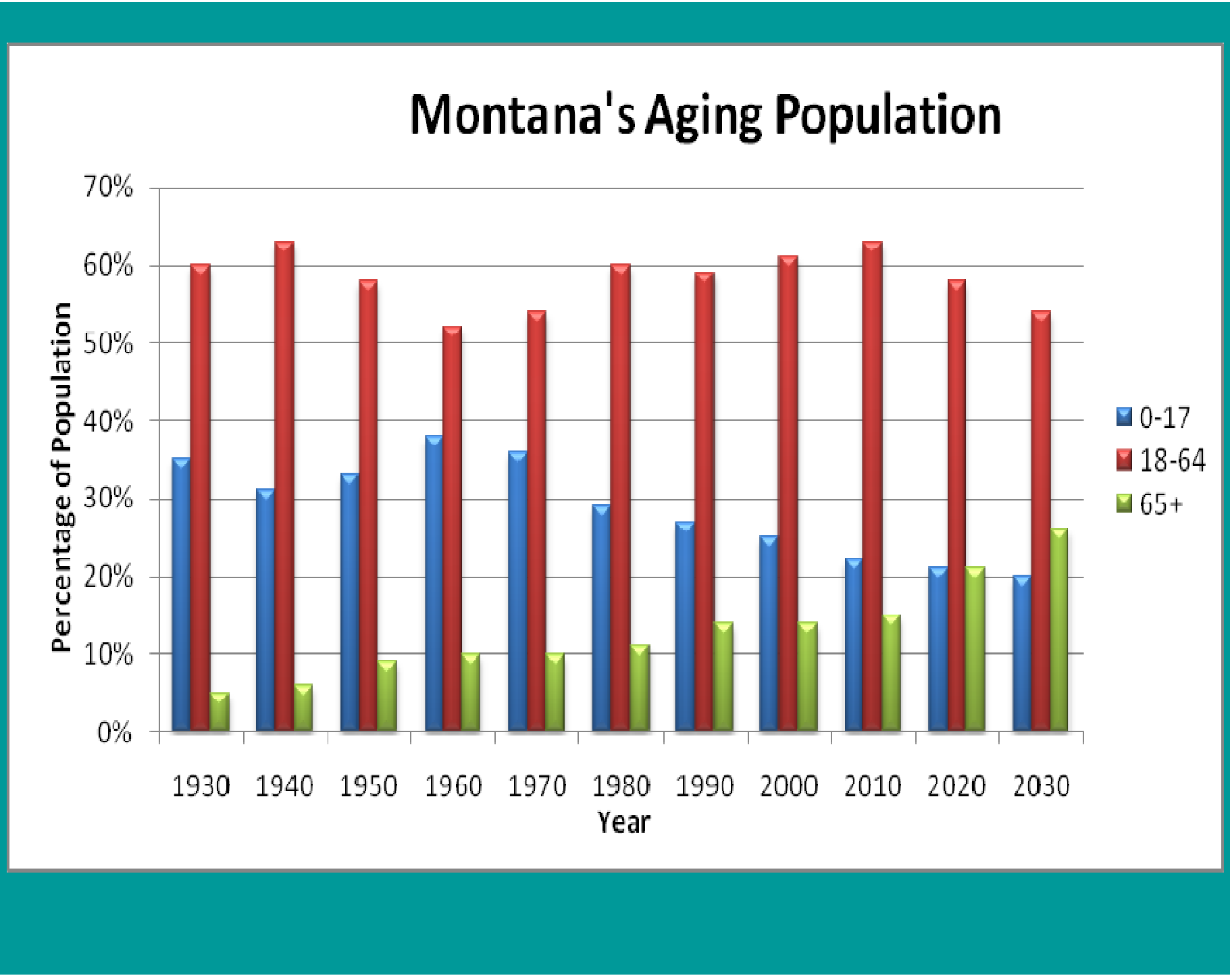
Figure 10. Proportion of population aged 60 or over: world and development regions, 1950-2050



From **World Population Ageing: 1950-2050**

United Nations Department of Economic and Social Affairs **Population Division**

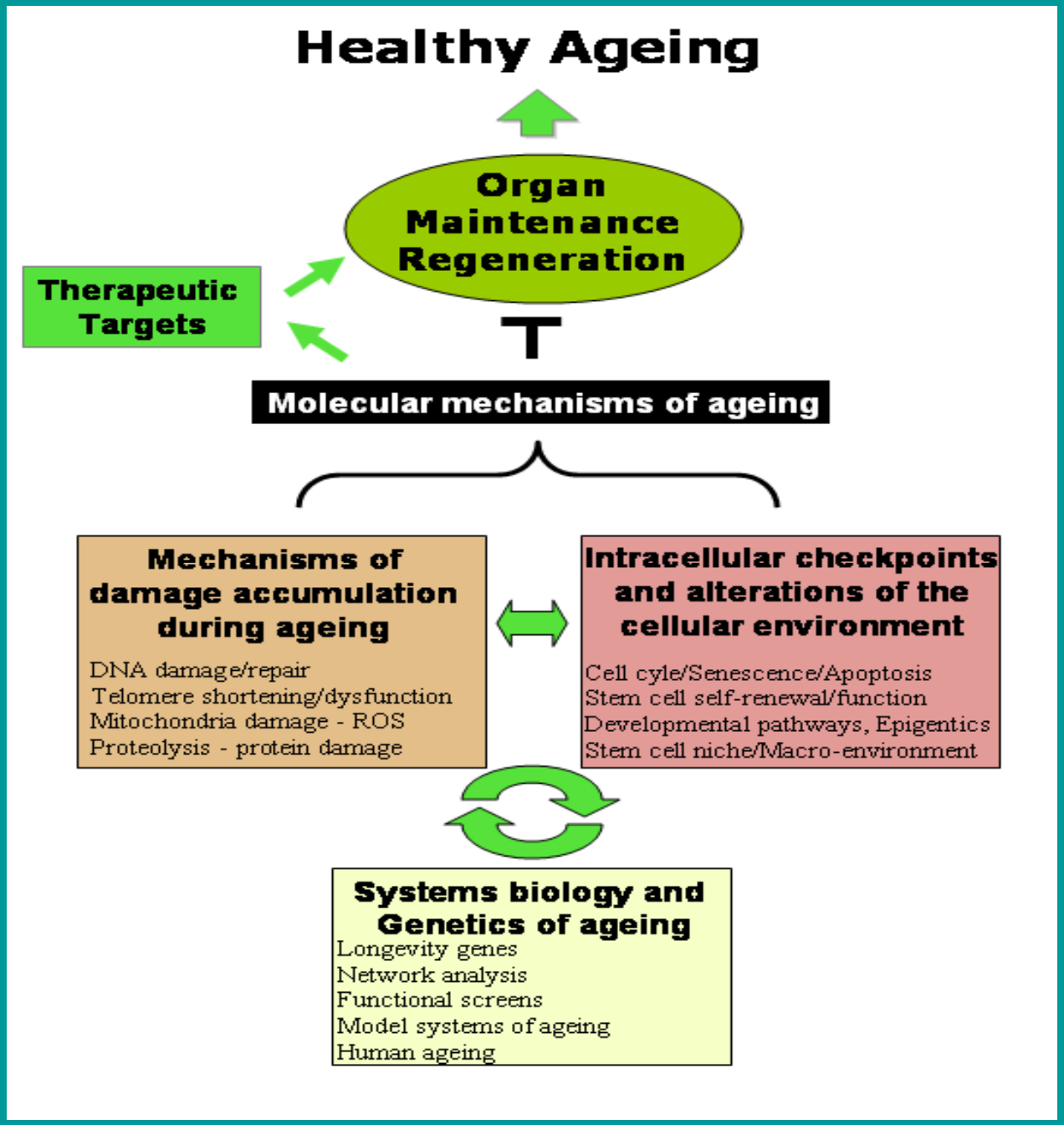
http://www.un.org/esa/population/publications/worldageing19502050/

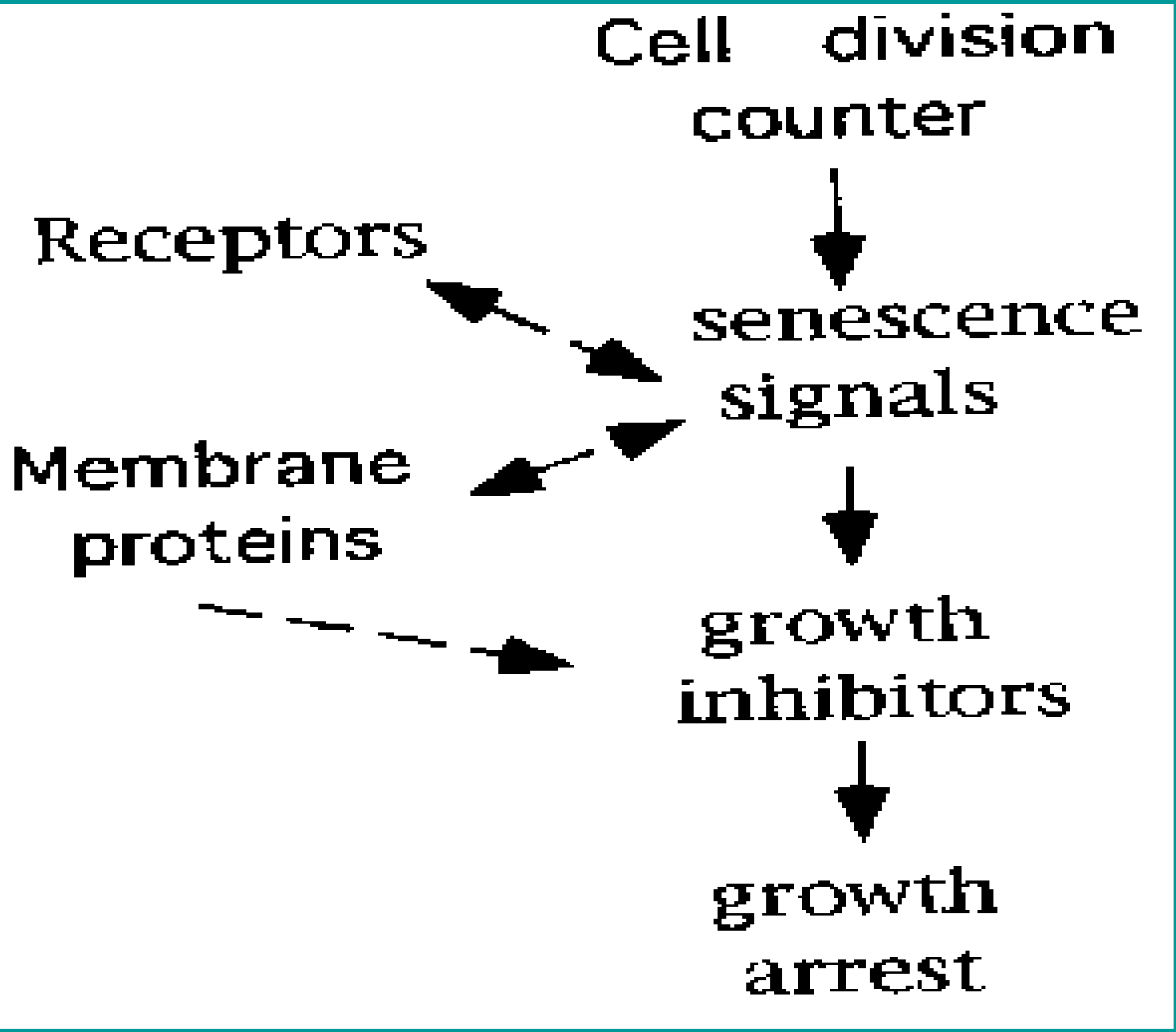

Montana's Aging Population
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Population
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020
2030
Year
0-17
18-64
65+

The process of aging can be characterized by :

1. Disorganization and determination
2. Progression
3. Internal mechanisms
4. Universal mechanisms

Who is older?


Healthy Ageing
Organ Maintenance Regeneration
Therapeutic Targets
Molecular mechanisms of ageing
Mechanisms of damage accumulation during ageing
DNA damage/repair
Telomere shortening/dysfunction
Mitochondria damage - ROS
Proteolysis - protein damage
Intracellular checkpoints and alterations of the cellular environment
Cell cyle/Senescence/Apoptosis
Stem cell self-renewal/function
Developmental pathways, Epigentics
Stem cell niche/Macro-environment
Systems biology and Genetics of ageing
Longevity genes
Network analysis
Functional screens
Model systems of ageing
Human ageing


Cell division counter
Receptors
senescence signals
Membrane proteins
growth inhibitors
growth arrest

Cellular aging:

1. Mitotic

every generation of cells has the capacity for aging

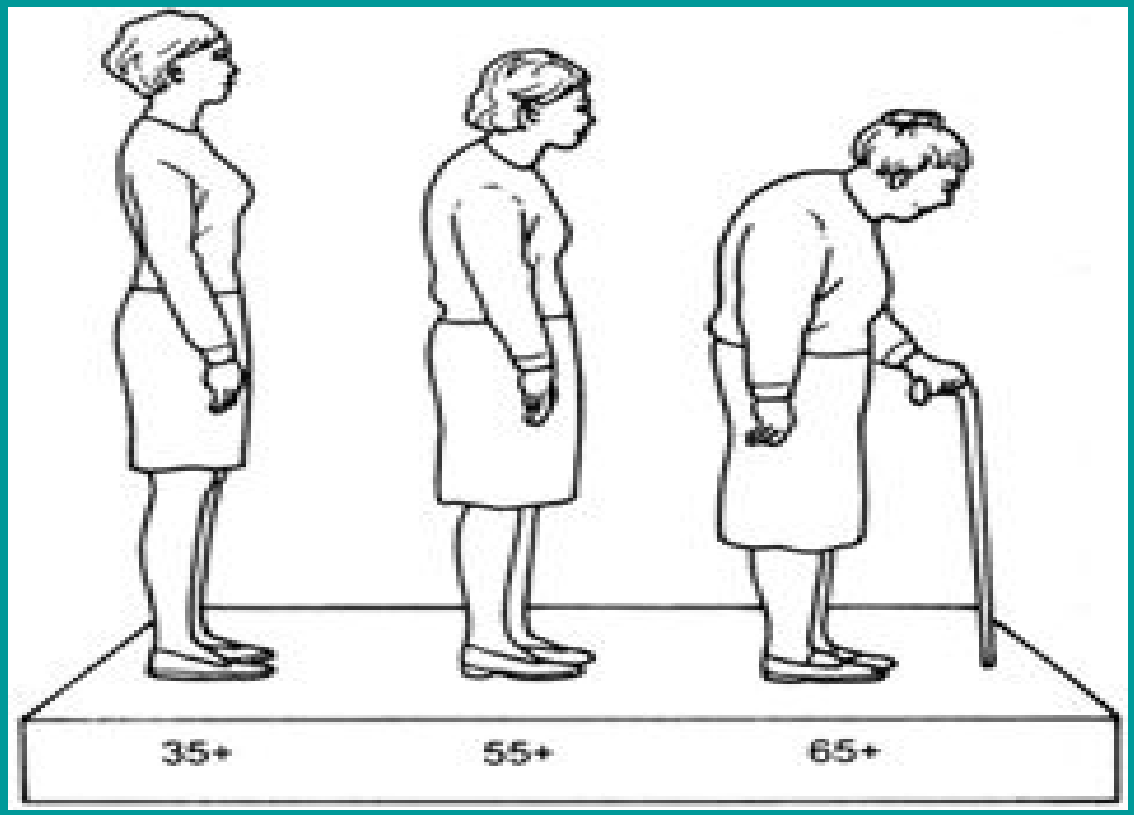
2. Postmitotic

neurons and cardiomyocites do not divide and grow with the body

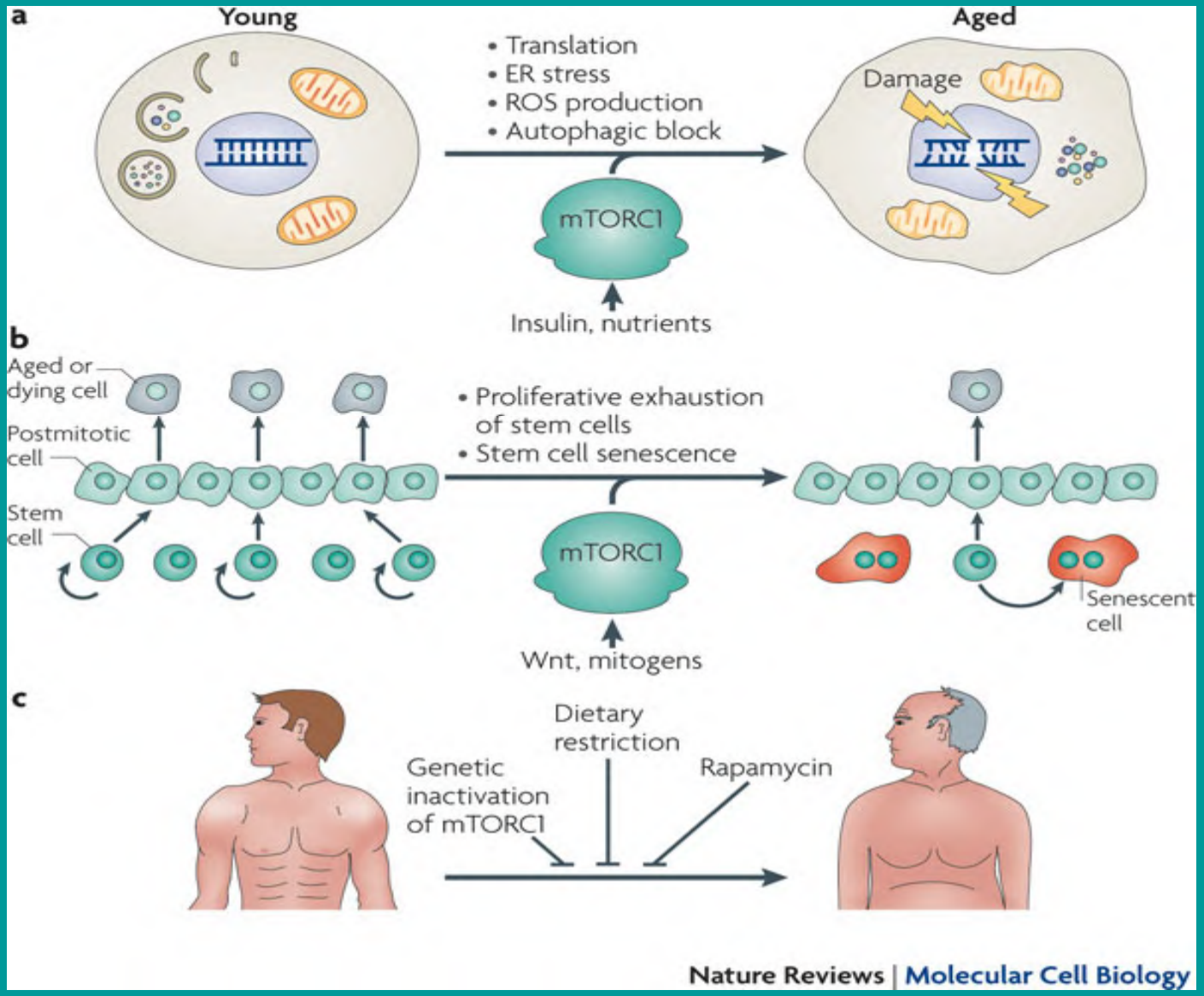
Segments of life

Evolutive segment (till 20 - 30 years)

Involutive segment (from 20 – 30 years)



Cellular and Molecular Aging



Cells eventually lose their ability to divide.

This limit to cellular replicative capacity (Hayflick's limit or phenomenon) can be demonstrated in fibroblasts.

The fibroblasts divide only until they are dense enough to contact each other--a phenomenon called contact inhibition.

If diluted, the fibroblasts divide again until maximum density is reached.

This process can be repeated; however, after about 50 divisions, the fibroblasts stop dividing regardless of their density.

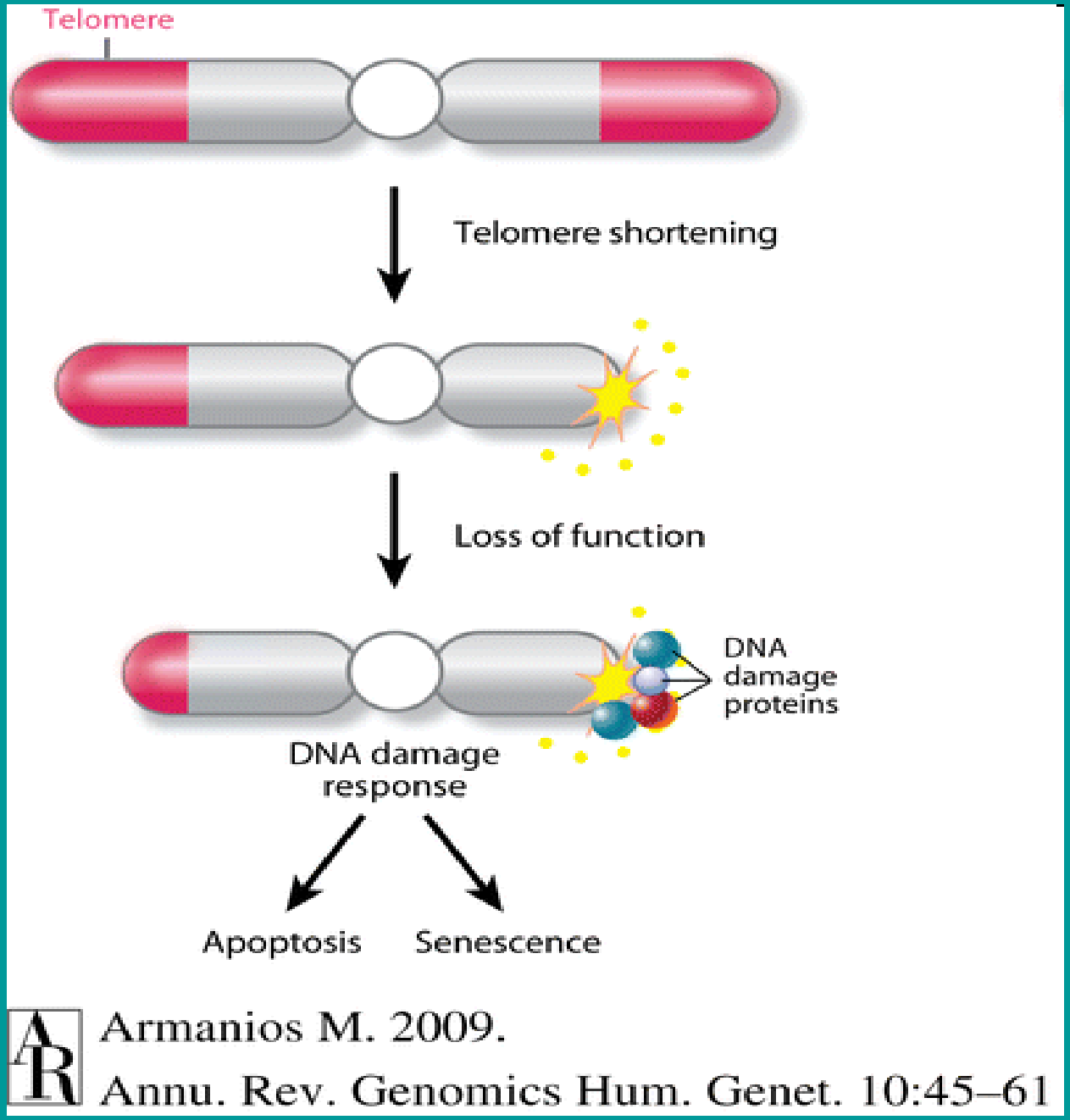
Studies have shown that the loss of replicative capacity does not depend on the total time cells are cultured (chronologic age) but on the number of divisions (biologic age).

When cells divide so many times that they cannot divide again, they enlarge and exist for some time before they gradually die.

One biologic mechanism for Hayflick's limit is understood.

Telomeres (stretches of DNA at the end of chromosomes) are used as handles to move chromosomes during the telophase of meiosis.

Telomeres are irreversibly shortened each time a cell divides. When they become too short, the cell can no longer divide.



Armanios M. 2009.

Annu. Rev. Genomics Hum. Genet. 10:45–61

Mechanisms other than telomerase shortening may be involved in senescence.

For example, messenger RNA (mRNA) transferred from senescent cells into young cells stops cell division in the young cells.

The mRNA acts as a gerontogene (a gene that normally reduces life span), whose function may resemble that of a tumor suppressor gene.

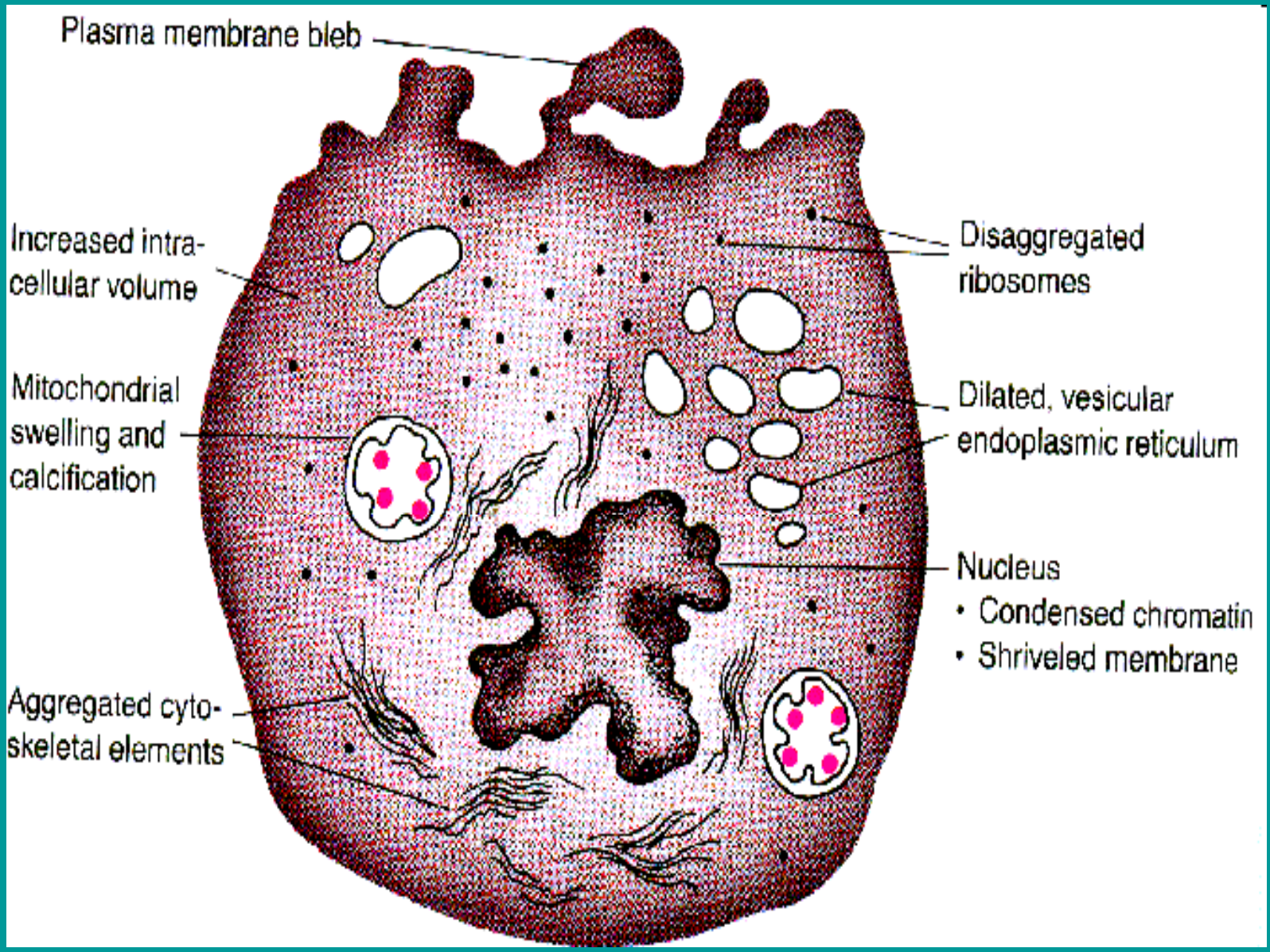
Mutations in gerontogenes may extend the number of divisions in cells, which can be expected to increase life span; however, certain mutations in gerontogenes lead to uncontrolled cell division, cancer, and often death of the organism.

Necrosis and apoptosis:

Cell death may occur by necrosis or apoptosis. Necrosis is due to physical or chemical insults (eg, metabolic inhibition, ischemia) that overwhelm normal cellular processes and make the cell nonviable.

In necrosis, loss of ion gradients across the cell membrane leads to an influx of Ca and other ions, which triggers proteolysis and rupture of organelle membranes.

Necrosis is a purely entropic phenomenon (characterized by a tendency to move toward randomness or disorder) due to loss of the cell's ability to transform external energy and perform normal functions.


Plasma membrane bleb
Increased intra-cellular volume
Mitochondrial swelling and calcification
Aggregated cyto-skeletal elements
Disaggregated ribosomes
Dilated, vesicular endoplasmic reticulum
Nucleus
• Condensed chromatin
• Shriveled membrane

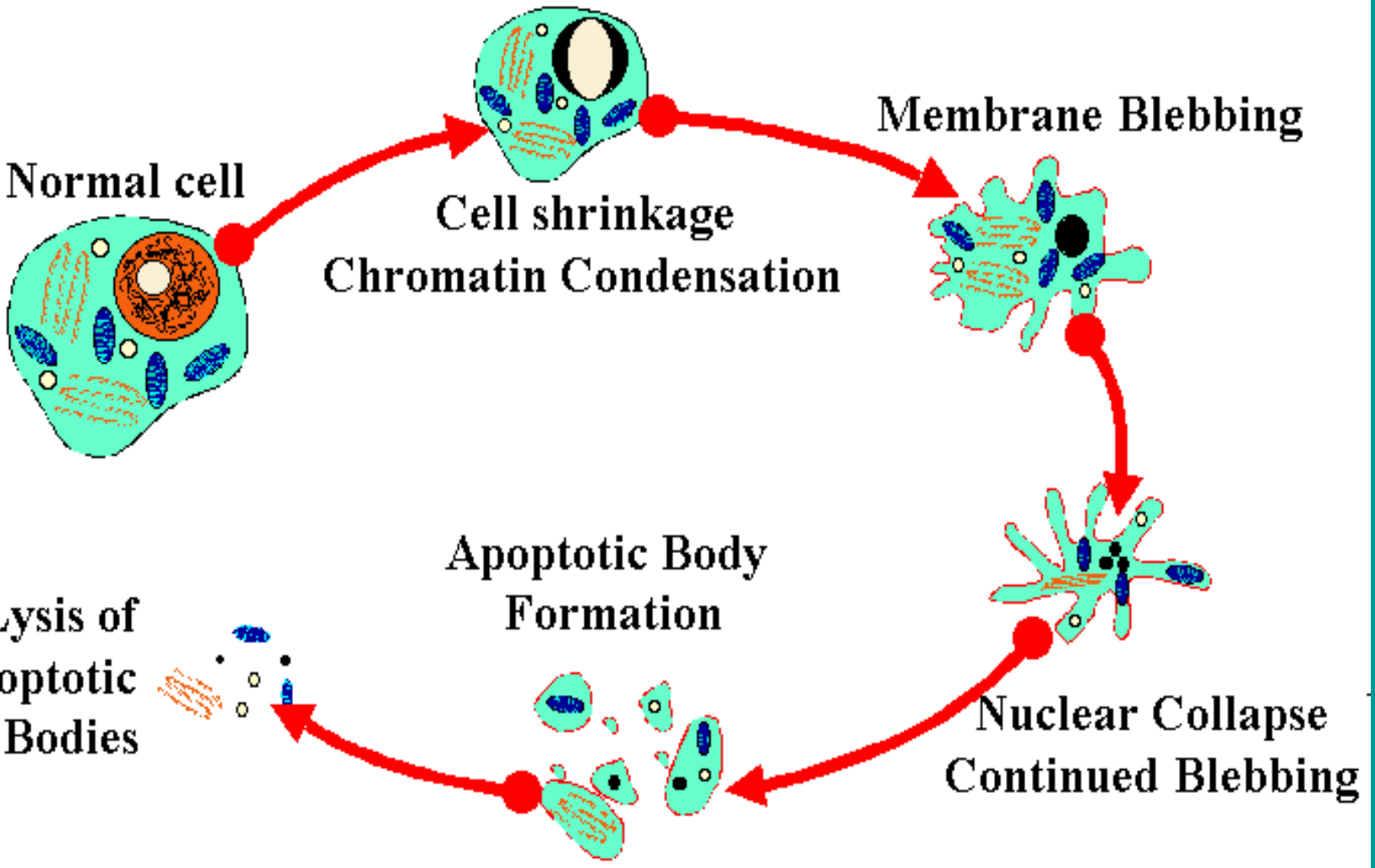
In contrast, apoptosis is a genetically determined, regulated, orderly process by which a cell essentially commits suicide; usually, the stimulus for apoptosis is a physiologic signal or a very mild insult.

A defining feature of apoptosis is fragmentation of the cell's DNA, produced by regulated activation of deoxyribonuclease.

Several other biochemical processes that also lead to cell death are simultaneously induced.

Apoptosis is essential for normal development and remodeling but has also been implicated in several age-related diseases, including Alzheimer's disease.

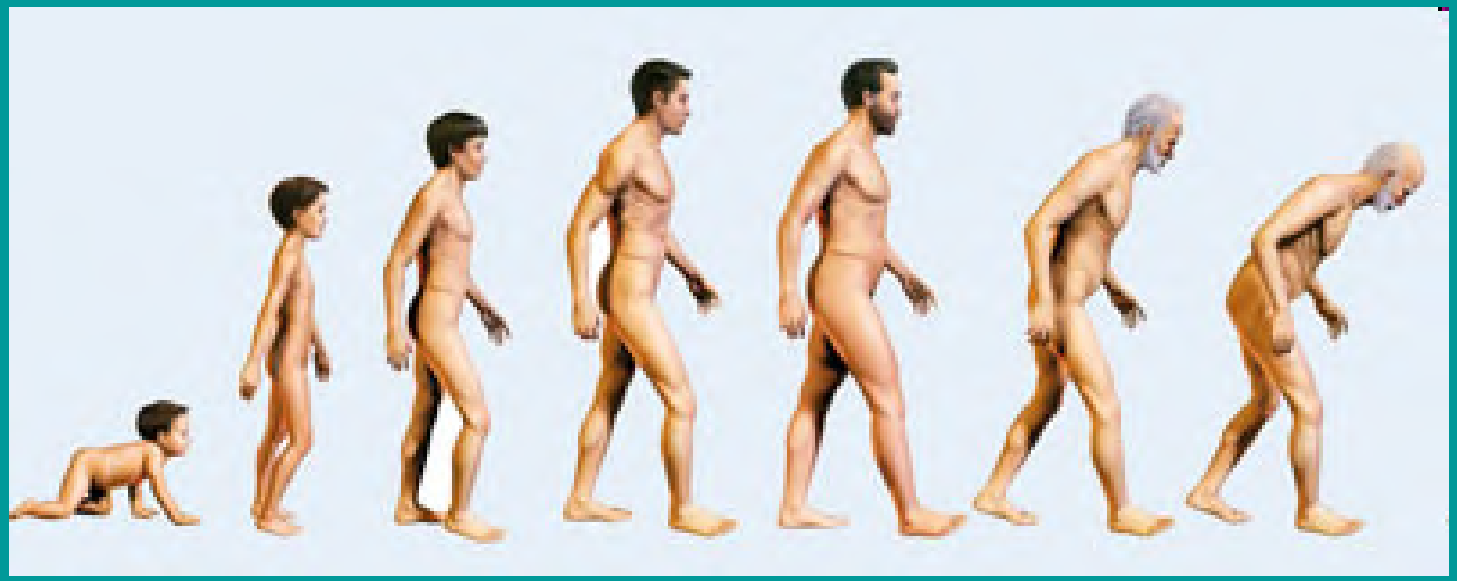
Apoptosis
(Programmed Cell Death)



Identifying the primary process involved in cell death (necrosis or apoptosis) during aging helps determine:

- whether aging is considered the result of entropic processes (if due primarily to necrosis)
- or of relatively simpler, more regulated processes (if due primarily to apoptosis).

Theories of Aging



Theories of Aging

- Programmed aging
  - Limited number of cell divisions or neuroendocrine stimuli from brain or endocrine glands stop at certain age
- Inefficient DNA repair
  - Over time proportion of cells carrying abnormal DNA increases and tissue function impaired; nuclear & mitochondrial DNA
- Free radical damage
  - Decreased scavenging systems
- Failure of protein catabolism
  - Inefficiency
- Summation of cumulative damage sustained throughout life to any systems
  - E.g. DNA damage, protein modification, free radical damage, or disease

Rate of living theory:

the rate of living theory is related to the idea that free radicals and other metabolic by-products play a role in senescence.

However, studies of metabolic rates have shown wide variation in the correlation between size and longevity.

Weak link theory:

This theory posits that a specific physiologic system--usually the neuroendocrine or immune system--is particularly vulnerable (presumably to entropic processes) during senescence.

Failure of the weak system accelerates dysfunction of the whole organism.

Failure of the neuroendocrine system would be expected to produce severe impairments in homeostatic systems, including loss of reproductive function and metabolic regulation, which occur with aging.

Failure of the immune system would be expected to produce an increased susceptibility to infection.

However, there is little evidence that failure of either system directly contributes to age-related diseases or to mortality.

In fact, recent studies indicate that neuroendocrine overactivity (eg, of the sympathetic nervous system or the insulin-like pathway), rather than failure, may drive certain aspects of the aging process.

Error catastrophe theory:

This theory posits that errors in DNA transcription or RNA translation eventually lead to genetic errors promoting senescence.

Master clock theory:

This theory is one of the oldest theories of aging and no longer has much credibility; it states that aging is under direct genetic control.

Individual variation develops because of maladaptation, exposure, and lifestyle.

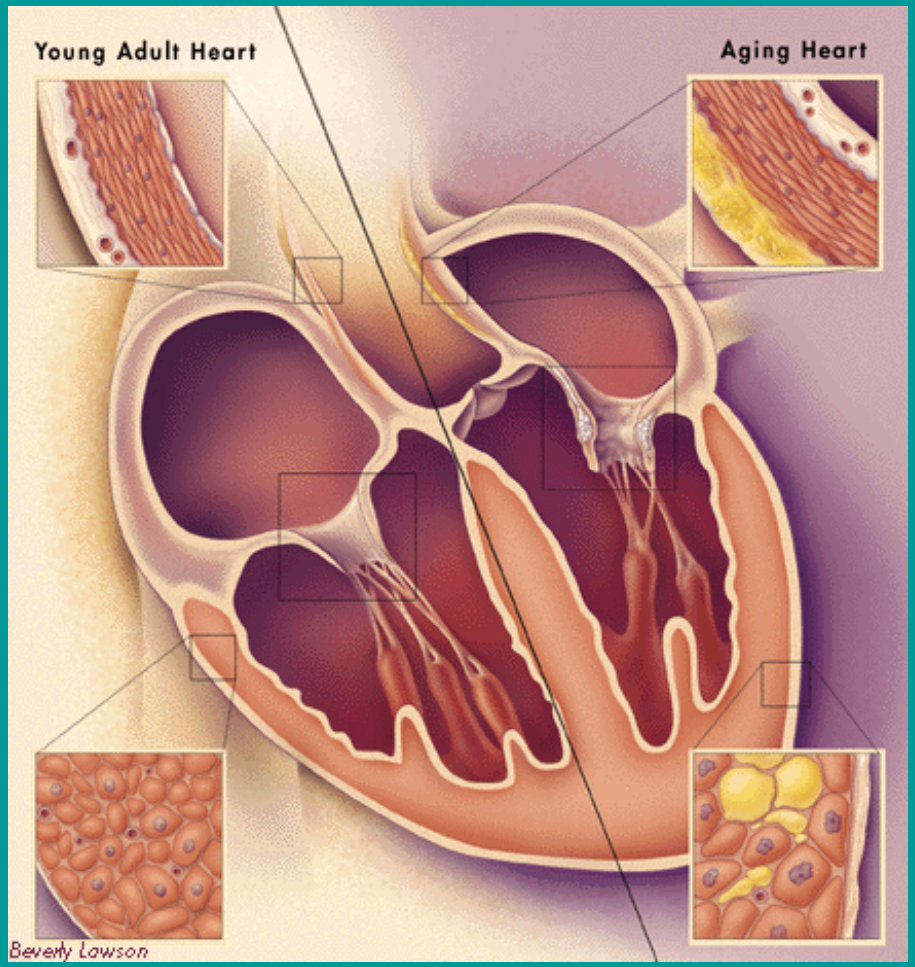
Exactly what controls the rate of aging is unknown.

It could be a gene that controls telomere shortening or some other process of cell division, or it could be genetic control of another cellular process not involved in division, such as DNA repair, resulting in apoptosis.

Changes caused by aging

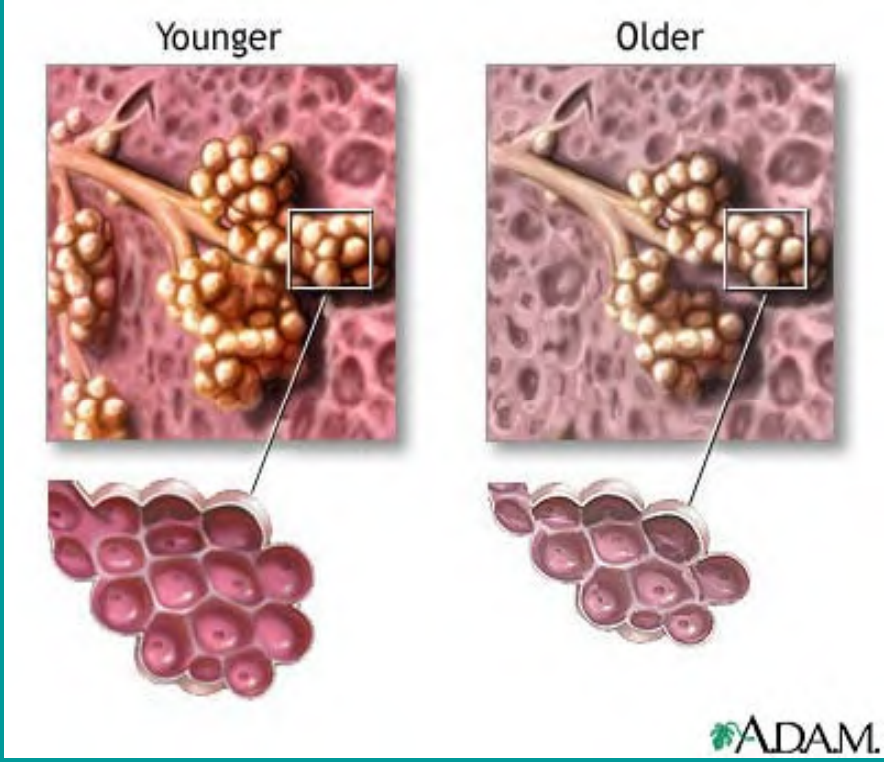
Changes in the cardio-vascular system:

- atrophy of the heart muscle;
- calcification of the heart valves;
- loss of elasticity in artery walls (arteriosclerosis);
- intra-artery deposits (atherosclerosis).
- decreased cardiac output, baroreceptor sensitivity and SA node automaticity.
- reduced blood flow which results in reduced stamina, reduced renal and hepatic function and less cellular nourishment.
- impaired blood pressure response to standing, volume depletion and heart blocks.



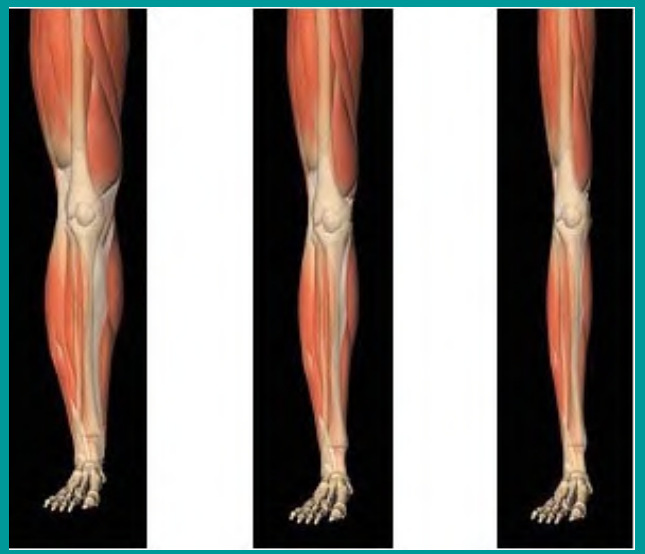
Changes in the respiratory system:

- the airways and lung tissue become less elastic with reduced cilia activity.
- decreased oxygen uptake and exchange.
- muscles of the rib cage atrophy, reducing the ability to breathe deeply, cough and expel carbon dioxide.
- ventilation/perfusion mismatch and decreased PO2.
- this leads to decreased stamina with shortness of breath and fatigue.



Changes in musculo-skeletal system:

- generalized atrophy of all muscles accompanied by a replacement of some muscle tone and strength.
- reduced ability to breathe deeply and reduced gastro-intestinal activity which can lead to constipation or bladder incontinence, particularly in women.
- calcium is lost and bones become less dense.
- osteoporosis and a reduction of weight bearing capacity, leading to the possibility of spontaneous fracture.
- thinning of the vertebrae can calcify, resulting in postural changes.
- arthritis, the degenerative inflammation of the joints, is the most common chronic condition in the elderly.



Changes in the gastrointestinal system:

- reduction in the production of hydrochloric acid, digestive enzymes and saliva.
- gastrointestinal distress, impaired swallowing and delayed emptying of the stomach.

The breakdown and absorption of foods may also be impaired, sometimes resulting in deficiencies of vitamin B,C ands K or in extreme cases, malnutrition.

Changes in the metabolic system:

The metabolic system
is responsible for changing food into energy.

After age 25,
everyone experiences approximately a 1% decrease per year
in their metabolic rate.

This overall slowing results in food
being less well absorbed and utilized.

There is a decrease in the overall metabolism of drugs

Sensory changes with **aging**:

Changes in vision:

- In the fourth decade, the pupil begins to decrease in size and there is decreased response to light.

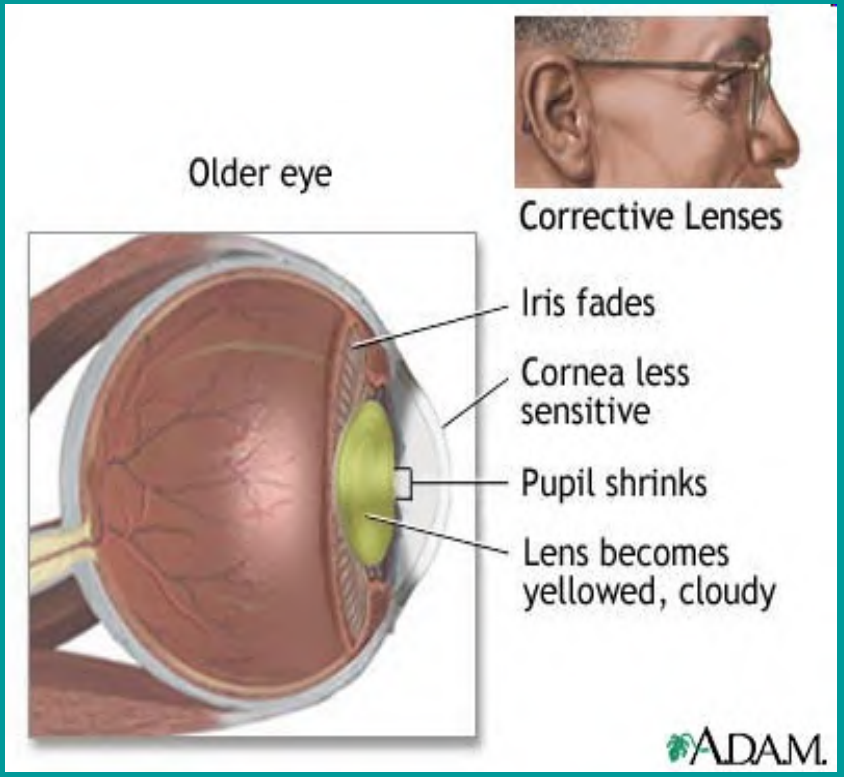
- Because of these changes, older people require three times the amount of illumination to see as compared to a younger person.

- Focusing takes longer with an increase in near sightedness, making small print harder to read.
- There is loss of accommodation which makes reading and close work difficult.

- This condition, which is known as presbyopia, can be corrected by wearing glasses with convex lenses.

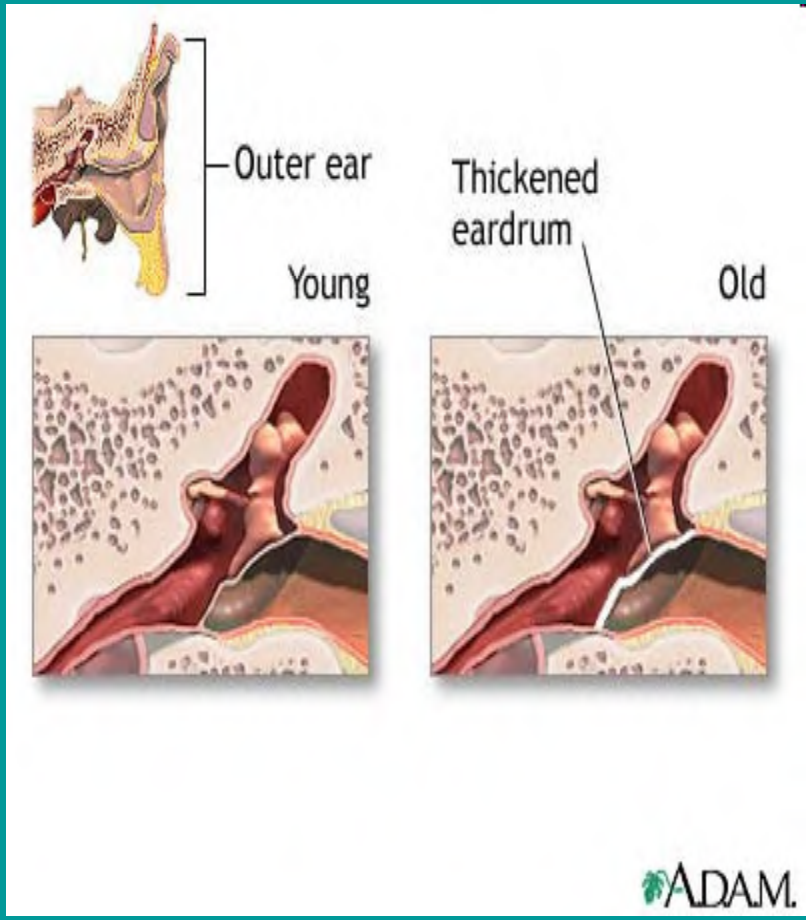
- There is thickening and yellowing of the lens of the eye.

- This results in light diffraction, increased sensitivity to glare, decreased depth perception and more difficulty distinguishing pastel colors, especially blues and greens



Changes in hearing:

- There is a decrease in sensitivity to high frequency tones and decreased discrimination of similar pitches because of changes in the bones and cochlear hair cells of the inner ear.
- Approximately 30% of all elderly persons have some hearing impairment.
- It is an invisible disability which is often covered up or denied by a person who may then be mislabeled as senile, dumb or uncooperative

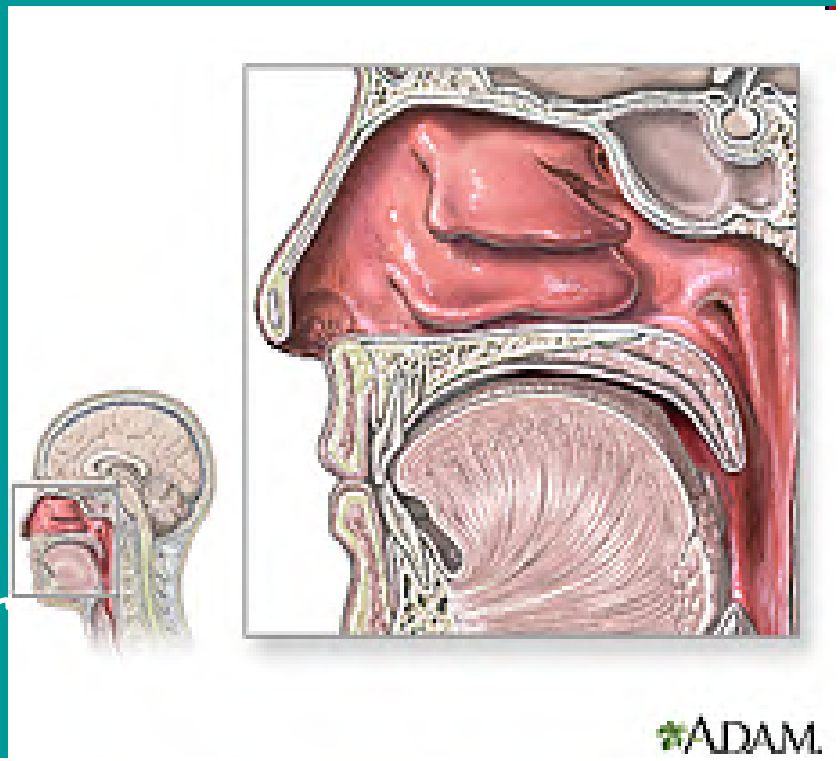


Changes in taste and smell:

- Taste and smell are interrelated and important for eating as well as checking for hazards in the environment such as spoiled food, smoke and fumes.

- Older adults experience some decline in the ability to taste resulting from a reduction in the total number of taste buds, especially after the age of 80.

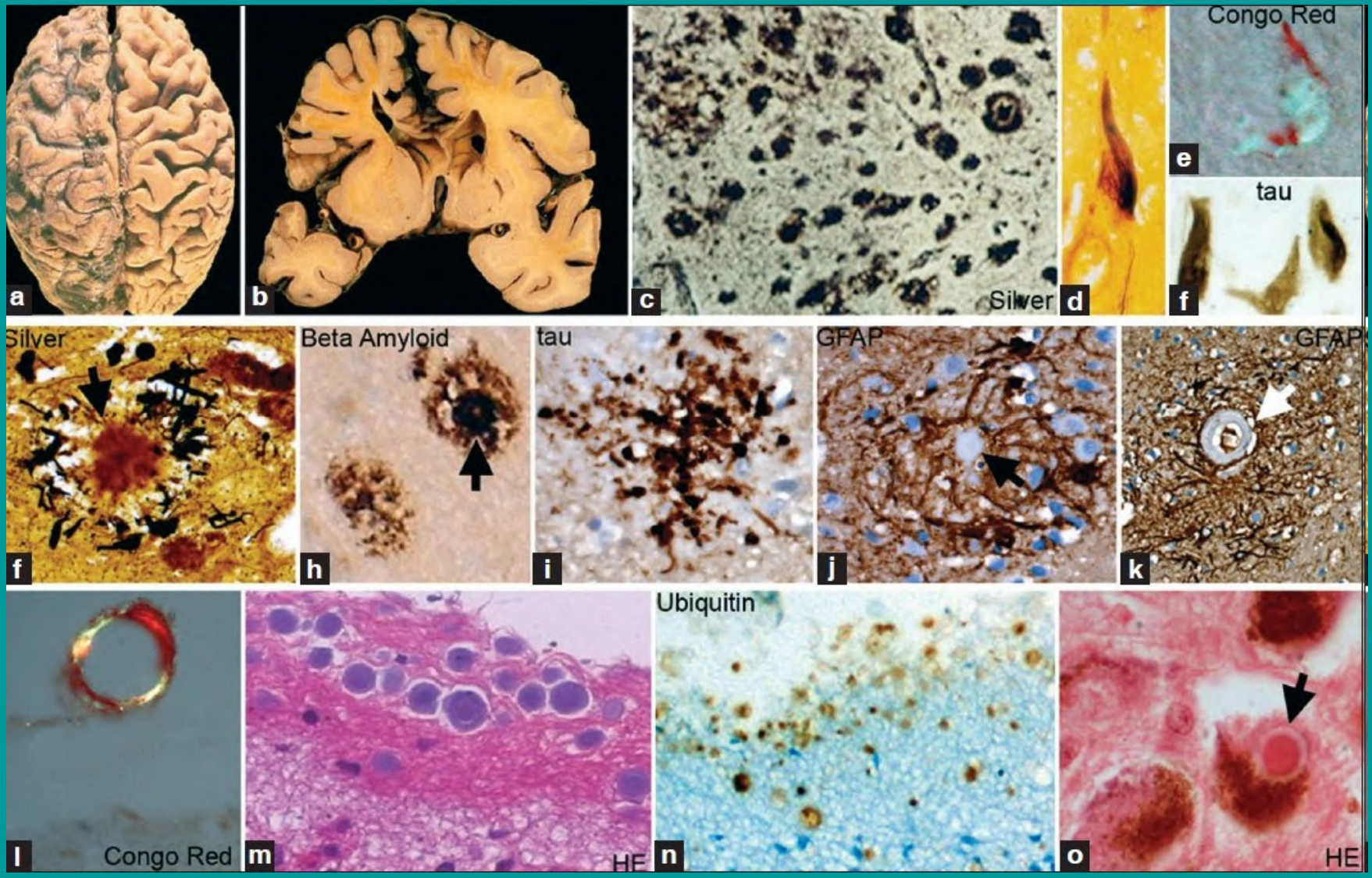
- Some individuals also experience a decline in their sense of smell, but this is usually because of abnormal conditions such as blockage or disease of the olfactory receptors in the upper sinus



Cognitive changes associated with aging:

- After age 25, everyone loses nerve cells.
- Gradually over time, this results in a reduced efficiency of nerve transmission which affect response time and coordination.
- These changes may also affect sleeping patterns by decreasing the length of total sleep time and REM sleep.
- In spite of these anatomical and **physiological** changes in brain, studies have found evidence of limited impairment of actual intellectual functioning associated with the **aging** process.
- Intellectual ability is one the factors affecting functioning in later life.

- The various changes in cognition are:


a
b
c
Silver
d
Congo Red
e
tau
f
Silver
f
Beta Amyloid
h
tau
i
GFAP
j
GFAP
k
l
Congo Red
m
HE
Ubiquitin
n
o
HE

Effect on intelligence:

Intelligence generally is associated with a range of abilities that allow us to make sense of our experiences:

- the ability to comprehend new information,
- the ability to think abstractly,
- the ability to make rational decisions,
- spatial ability,
- numerical ability,
- verbal fluency, etc.

Some abilities (e.g., the ability to think abstractly) are biologically determined and are known as "fluid intelligence."

Other intellectual abilities (e.g., verbal fluency) reflect the knowledge and skills a person has gained through life experience and known as "crystallized intelligence."

Intelligence tests have demonstrated a pattern of age-related changes in intellectual functioning.

These tests show somewhat poorer performance by older people on tests of fluid intelligence, but little or no difference on tests of crystallized intelligence.

Effect on learning and memory:

- Most persons experience a modest increase in memory problems as they get older, particularly with regard to the ability to remember relatively recent experiences.

- There is impairment of the ability to accumulate new information and to retrieve existing information from memory.

- There is little decline in the ability to store new information once it is learned

Personality changes associated with aging:

Whereas basic personality traits may remain rather stable throughout adulthood, relatively predictable shifts may occur in other aspects of a person's personality.

One of the best documented personality changes in adulthood is an increased preoccupation with one's inner life, including greater attention to personal feelings and experiences and reduced extraversion.

A second domain in which age-related changes have been reported is gender role identity.

With advancing age, men and women appear to become more similar in terms of their values and personality styles.

Studies in a number of different cultures have found that men tend to become more nurturing, expressive and affiliation-seeking as they grow older, whereas women tend to become more instrumental and achievement-oriented

Some of the physiological modifications are the indicators of the aging process and on their base we can appreciate the biological age of a person.

In ideal condition the biological age is the same with the chronological age – the normal or orthogenetic aging.

If the biological age is bigger than the chronological one – we can speak about **an accelerate aging**,
but if it is smaller – **the late aging**.

The biological age and the rhythm of aging depend on:

- The genetic factors;

- Environmental factors;

- Pathological factors (infection, toxic, degenerative, posttraumatic diseases).

The pathologic factors lead to the accelerated aging, and because of the new morpho-functional changes generated by some pathology, the aging in these cases is a pathologic one.

The aging indicators are named markers or criteria.

The indicator selection is made according to some criteria:

- The simple possibility of detection

- Their correlation with the aging process beginning from the period of 40-45 years old

- Their objective character (their credibility)

- The possibility to a quantitative appreciation.

Using these criteria some evaluation scores were adapted.

There some characteristic "criteria" for every period of aging.

In presenescence they are due to some skin and hair changes, than – to the cardiovascular, auditive visual changes.
After 65 years – the changes of cardiovascular, nervous systems and of the analisators.
The senescence after 75 years is dominated of the cardiovascular and osteolocomotor changes.

Canadian classification (1998)

65-74 years old – the young elderly;

75 – 84 years old – the adult elderly;

Older than 85 years – the old elderly.