Aging is the stage of ontogenesis. Biological and genetic aspects of human aging.

Azerbaijan Medical University

Department: Medical biology and genetics

Presented by Assistant professor Suleymanova Leyla

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Stages (periods) in ontogenesis

- **Ontogenesis,** or **ontogeny** is the origination and development of an organism from the time of fertilization of the egg to the organism's mature form and complete with normal physiology death.
- The main stages (periods) in ontogenesis:

1.Prenatal, including the development of sex cells (gametogenesis), fertilization and embryogenesis (zygote, cleavage, blastula, gastrula and neurula). The end of the prenatal period is birth.

2. Postnatal - begins from birth until natural death.

Periods of postnatal ontogenesis

	female	male
Newborn	1-10 days	1-10 days
Infancy	10 days-1 year	10 days-1 year
Childhood	1-11 years	1-12 years
Teenagers	12-15 years	13-16 years
Youth	16-20 years	17-21 years
Adult	21-55 years	22-60 years
Old age	56-74 years	61-74 years
Senility	**75-90 years**	**75-90 years**
Longevity	90 years and more	90 years and more

Gerontology is the science about aging

- **Gerontology** is the study of the social, cultural, psychological, cognitive, and biological aspects of aging.
- **Biogerontology** is the sub-field of gerontology concerned with the biological aging process.
- **Biomedical gerontology**, also known as experimental gerontology and life extension, is a sub-discipline of biogerontology that endeavors to slow, prevent, and even reverse aging in both humans and animals.

Theories of aging

- **Stochastic theories:**
  - Wear and tear theories
  - Accumulation theories
  - Free radical theory
  - DNA damage theory
  - Cross-linking theory
- **Genetic theories**
- **General imbalance**
  - Immunological theory
- **Social theories of aging**

Theories of aging

- **Stochastic theories** of aging is the suggestion that aging is caused by small changes in the body over time and the body's failure to restore the system and mend the damages to the body.

- Wear and tear theories of aging suggest that as an individual ages, body parts such as cells and organs wear out from continued use.

- Accumulation theories of aging suggest that aging is bodily decline that results from an accumulation of elements, whether introduced to the body from the environment or resulting from cell metabolism.

- The free-radical theory of aging proposes that this damage cumulatively degrades the biological function of cells and impacts the process of aging.

Theories of aging

- DNA damage theory DNA damage has been one of the many causes in diseases related to aging.

- The cross-linking theory proposes that advanced glycation end-products (stable bonds formed by the binding of glucose to proteins) and other aberrant cross-links accumulating in aging tissues is the cause of aging.

- **Genetic theories** of aging propose that aging is programmed within each individual's genes. According to this theory, genes dictate cellular longevity. Programmed cell death, or apoptosis, is determined by a "biological clock" via genetic information in the nucleus of the cell.

Theories of aging

- **General imbalance theories** of aging suggest that body systems, such as the endocrine, nervous, and immune systems, gradually decline and ultimately fail to function.

- The immunological theory of aging suggests that the immune system weakens as an organism ages. This makes the organism unable to fight infections and less able to destroy old and neoplastic cells. This leads to aging and will eventually lead to death.

Theories of aging

- **Social theories of aging**

- Activity theory According to this theory, older adults' self-concept depends on social interactions. In order for older adults to maintain morale in old age, substitutions must be made for lost roles. Examples of lost roles include retirement from a job or loss of a spouse.

- Disengagement theory According to this theory, older adults and society engage in a mutual separation from each other. An example of mutual separation is retirement from the workforce. A key assumption of this theory is that older adults lose "ego-energy" and become increasingly self-absorbed.

Senility

- **Senility** is the period of a person's life from the loss of the body's ability to continue the race to death. It is characterized by deterioration of health, mental abilities, extinction of body functions.
- Old age is a natural period of age development, is the final stage of ontogenesis.
- People are considered old because happen some changes in their activity in social role.

Aging

- Aging is the process of becoming older.
- Aging is an biological destructive process, leading to a gradual decrease in the adaptive capacity of the organism.
- It is characterized by the development of the so-called age pathology and an increase in the probability of death.

Aging

- Men and women aged from 55–60 to 75 years old are considered elderly, 75 years are old, and 90 years are longevity.
- It is assumed that the duration (specific) of a person's life is 92-95 ages.

Aging

All changes in metabolic rate and function, developing with age, refer to one of three types of changes:

- **Progressively decreasing** (reduced function of the heart, digestive and endocrine glands, memory, etc.).
- **Significantly unchanged** (blood sugar level, acid-base balance, etc.).
- **Progressively increasing** (activity of some enzymes, cholesterol, lecithin, etc.)
- Significant age-related differences in the reliability of homeostasis are detected with functional loads.

Aging

Heterochronicity – the difference in time of aging onset of certain tissues, organs, systems.

The start of organs aging :

after 20 years –cerebral organs;

after 30 years – kidneys, spleen;

after 40 years – skeleton, heart;

after 50 years – liver, gastrointestinal tract, lungs, muscles.

Thymus gland atrophy in humans begins between 13- 15 years, sex glands – in menopause (48-52 years for women), and some pituitary functions remain on high level until old age.

External signs of aging

- **Growth.** The flattening of the intervertebral discs with age and an increase in slouching leads to a reduction in the length of the body during aging.
- The most pronounced increase in stoop occur after 65 years, but it can appear after 40 years. Growth decreases occur after 60 years on average by 0.5–1 cm over the five-year period.

External signs of aging

- **Body mass.** Mass also decreases from the period of maturity to the elderly and senile age, and especially in long-livers. Age-related weight loss in men is more pronounced than in women.
- The amount of muscle tissue is greatest and relatively constant at 20–30 years old, then begins at first a weak, and later on all its increasing decline, especially after 50 years.

External signs of aging

- **Skin.** Age-related skin changes usually begin after 40 years. They especially affect the structure of the upper (epidermal) layer, which is thinned and flattened. By the age of 80, its thickness is 25% less than in 30 years. The temperature of the skin decreases, especially for long-livers. This is due to a general decrease in metabolic processes, but partly due to the deterioration of the blood supply and changes in the sweat glands.

External signs of aging

- **Skin.** Age-related changes in the skin is reflected in a change in the number of sweat glands. Due to the decrease in their number, the excretory function of the skin is weakened. Significant changes undergo also hair.
- Starting as early as 30 years, reduced the amount of hair, they turn grey as the hair follicles cells lose their ability to form pigment.

Aging of organ systems

- **Muscular system and skeleton.** On the part of the muscular system, there is a reduction in the force of contraction of the striated muscles, muscle atrophy, and rapid development of fatigue.
- The most common sign of aging in the age of 45–50 years old is bone loss - osteoporosis.
- Age-related osteoporosis is a universal general biological process that develops in humans.

Aging of organ systems

- **Muscular system and skeleton.** Bone density in men at the age of 70 years is 70% of normal density, in women - 60%.
- In addition to age, manifestations of osteoporosis are affected by endocrine disorders, malnutrition, reduced motor activity.

Aging of organ systems

- **Muscular system and skeleton.** For aging people, the phenomena of osteochondrosis are also typical. At the same time, destructive changes in the cartilage tissue of intervertebral discs are observed. At older ages, they occur in 83–98% of cases.
- Usually these changes occur in the cervical and lumbosacral (lumbosacral radiculitis) parts of vertebra.

Aging of organ systems

- **Nervous system.** Structural aging of the nervous system is manifested in a decrease in the number of nerve cells - neurons.
- This may occur slowly after birth, but a noticeable loss of them occurs rather late, starting at 50–60 years, and occurs unevenly in different areas of the brain of the elderly.
- The loss of neurons in the cerebral cortex of old people can reach 40–50% or more. For example, the brain weight of men 20–30 years old is on average 1394 g, and in 90 years it is only 1161 g.
- Age-related phenomena are also observed in the spinal cord and peripheral nervous system, as well as in all parts of the autonomic nervous system.

Aging of organ systems

- **Sense organs.** With age, significant disturbances occur in the functioning of the organs of sight and hearing, which significantly limits the adaptive abilities of a person.
- Taste is an evolutionarily ancient feeling that forms very early and persists into extreme old age.
- According to some reports, about 80% of people over 60 years old have a weakening of taste function, presumably the most to the sweet.
- Objectively, there is a decrease in the number of taste bulbs with age, starting from 45 years old, although compensatory processes are not excluded.

Aging of organ systems

- **The cardiovascular system.** Signs of aging of the cardiovascular system become noticeable after 40 years.
- Significant changes affect primarily the arteries that carry oxygen-rich blood. Lipids, especially cholesterol, are deposited in their walls, which leads to a decrease in vascular elasticity.
- Starting from the third decade, and especially after 60–65 years, calcium salts are deposited on the walls of blood vessels.

Aging of organ systems

- **The cardiovascular system.** As a result, there is a gradual decrease in the elasticity of the walls of the arteries, the ability to expand and contract, weakening blood flow.
- The blood flow through the vessels of the brain of a 75-year-old person is reduced by 20% compared with a 30-year-old person.
- With age, there are changes in the veins - increases the cross-sectional area, tortuosity. Particularly noticeable are the subcutaneous veins in the temples, neck, hands.

Aging of organ systems

- **The cardiovascular system.** Veins on the legs sometimes take the form of laces or nodules.
- Age-related changes affect the network of the smallest blood vessels - capillaries.
- The deterioration of the blood supply covers the most diverse systems of the body - the brain, muscles, internal organs.
- The general blood supply to tissues and organs is weakened, which leads to the development of fatigue in elderly and old people and an increase in blood pressure.

Aging of organ systems

- **The cardiovascular system.** Sclerotic changes occur in the heart muscle (myocardium).
- Changes begin at about 30 years old, they become especially pronounced after 40 years.
- In old age, the expansion and weakening of the heart is often noted, the contractile ability of the heart muscle is reduced, it grows connective tissue.

Aging of organ systems

- **Digestive system.** Aging of the digestive system, compared with other systems, is expressed quite moderately.
- The most pronounced age-related changes in the oral cavity. This is a weakening of the chewing muscles and bones of the facial region of the skull.
- There is a decrease in the size of the lower and especially the upper jaw, the change of the bite, the location of the teeth.

Aging of organ systems

- **Respiratory system.** Age-related changes in the respiratory system are associated with the destruction of interalveolar septa, which leads to a reduction in the respiratory surface.
- With age, connective tissue grows in the lungs, the efficiency of oxygen metabolism decreases.
- With aging, the total capacity of the lungs decreases, especially the vital capacity of the lungs, which by 75 years reaches only 56% of the level at the age of 30 years. Therefore, in old age, with strenuous activity occurs shortness of breath.

Aging of organ systems

- **Respiratory system.** The risk of inflammatory diseases of the bronchi and lungs increases, the supply of oxygen to the body worsens.
- The oxygen saturation of arterial blood also decreases. However, in old age there are also compensatory mechanisms for improving the function of the respiratory system, for example, an increase in respiration, leading to increased ventilation of the lungs.

Aging of organ systems

- **Genitourinary system.** In the process of aging, all organs of the excretory and reproductive systems are affected. The kidneys are reduced in mass, especially after 70 years. By old age, up to 1/3 –1/2 of the main morphofunctional units of the kidneys, nephrons are lost.
- In humans, the number of renal glomeruli progressively decreases with age that occur very early, but develop slowly.

Aging of organ systems

- **Genitourinary system.** In the reproductive system there is a decrease in the production of gametes and the formation of sex hormones.
- In women, oogenesis stops when they reach menopause, in men, the formation of high-grade spermatozoa is possible even in old age.

Aging of organ systems

- **Genitourinary system.** Changes in the hormonal profile of people in connection with the extinction of reproductive function is complex. Progressively decreases with age, the concentration of testosterone in men, and estradiol and progesterone in women.
- Both types of hormones are formed by organisms of both sexes, only in different quantities. These changes are accompanied by increased secretion of estradiol and progesterone in men and testosterone in women.

Manifestations of aging on molecular and cellular levels

The aging process captures all levels of the structural organization of the individual - molecular, cellular, tissue, organ.

Manifestations of aging on molecular and cellular levels

- **On molecular level:**

- down-regulation of transcriptional activity
- down-regulation of protein translation
- changes in activity of enzymes
- changes in formation, transport and use of energy
- decrease in the intensity of synthesis of a number of hormones

Manifestations of aging on molecular and cellular levels

- **On cellular level:**

- decrease the number of mitotic cells (Hayflick limit)

- decreases the sensitivity of cells to various growth factors and hormones

- intercellular relationships are broken

- accumulate substances, which at a young age are formed only in pathology (in particular, lipofuscin)

- amyloid accumulates between cells , resulting in the development of senile amyloidosis, manifested amyloidosis of the brain, heart, liver and pancreatic islets

- nuclear control over the cytoplasm is weakened (quantitative and qualitative changes in the relationship between the nucleus and the cytoplasm)

- decrease the number of mitochondria + decrease the efficiency of their functioning = decrease the specific metabolic rate

Manifestations of aging on molecular and cellular levels

- **On cellular level:**

- changes plasticity and permeability of plasma membrane

- changes in endoplasmic reticulum (number of ribosomes on its membrane as well as the number of polysomes in the cytoplasm reduced)

- the intensity of plastic processes decreases

-changes in the composition of lipids (cholesterol increase)

- decrease the number of ion channels

slows down the active transport

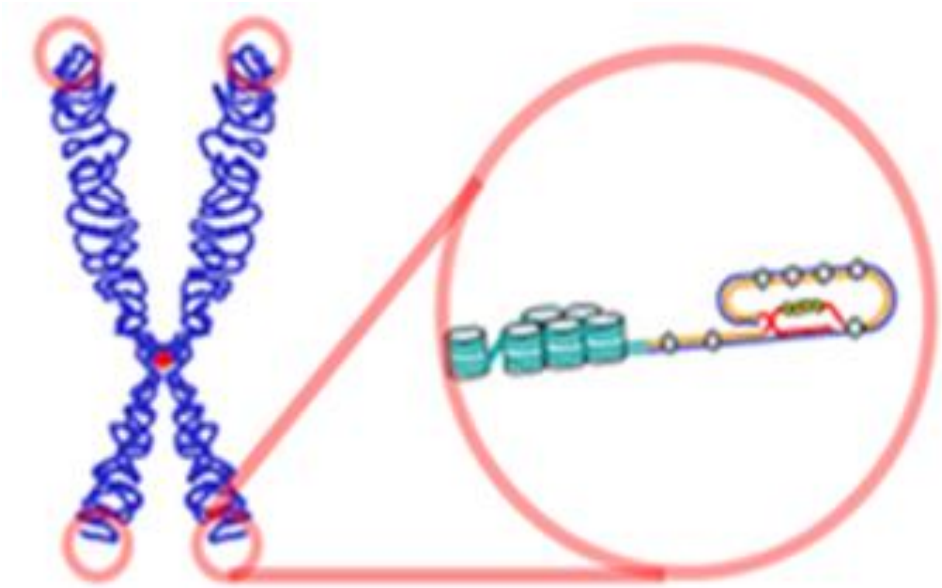
- decrease the delivery of O_2 to the cell

Replicative Aging of Somatic Cells

- **Replicative aging** is the limited number of divisions that a single cell can attain.
- The typical normal human somatic cell will divide between 50 to 70 times before experiencing senescence. As the cell divides, the telomeres on the ends of chromosomes shorten.
- The **Hayflick limit (**stop of cell division - it becomes senescent) is the limit on cell replication imposed by the shortening of telomeres with each division.

Replicative Aging of Somatic Cells

Telomeres are found at the termini of chromosomes. The end of a telomere inserts back into the main body of the telomere to form a T-loop.



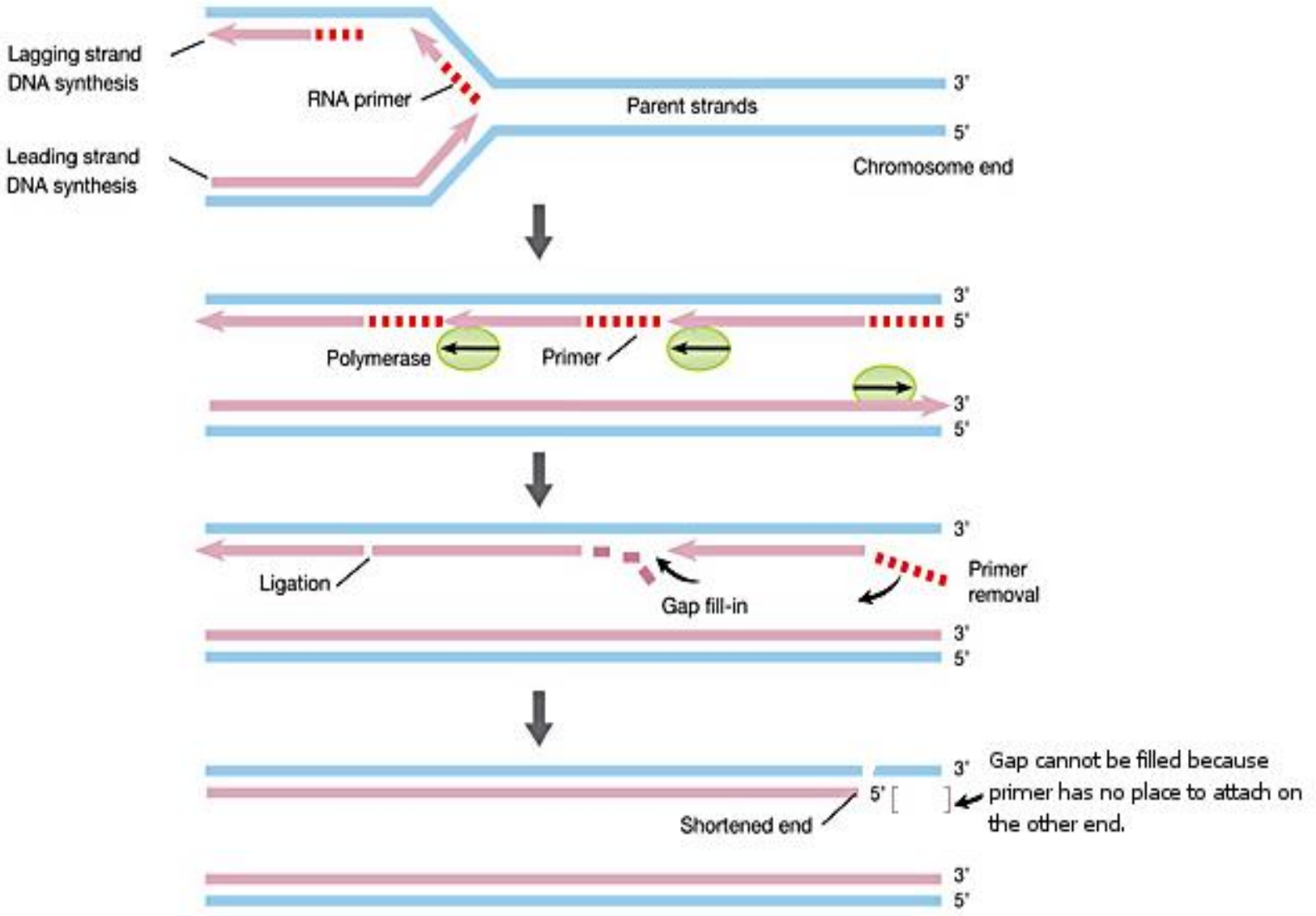
Replicative Aging of Somatic Cells

- It was found that the Hayflick limit correlate with the length of the telomere region at the end of chromosomes.
- During the process of DNA replication of a chromosome, small segments of DNA within each telomere are unable to be copied and are lost (In the early 1970s, Russian theorist Alexei Olovnikov first recognized that chromosomes could not completely replicate their ends). This occurs due to the uneven nature of DNA replication, where leading and lagging strands are not replicated symmetrically. The telomeric region of DNA does not code for any protein; it is simply a repeated code on the end region of linear eukaryotic chromosomes. After many divisions, the telomeres reach a critical length and the cell becomes senescent. It is a point that a cell has reached its Hayflick limit.

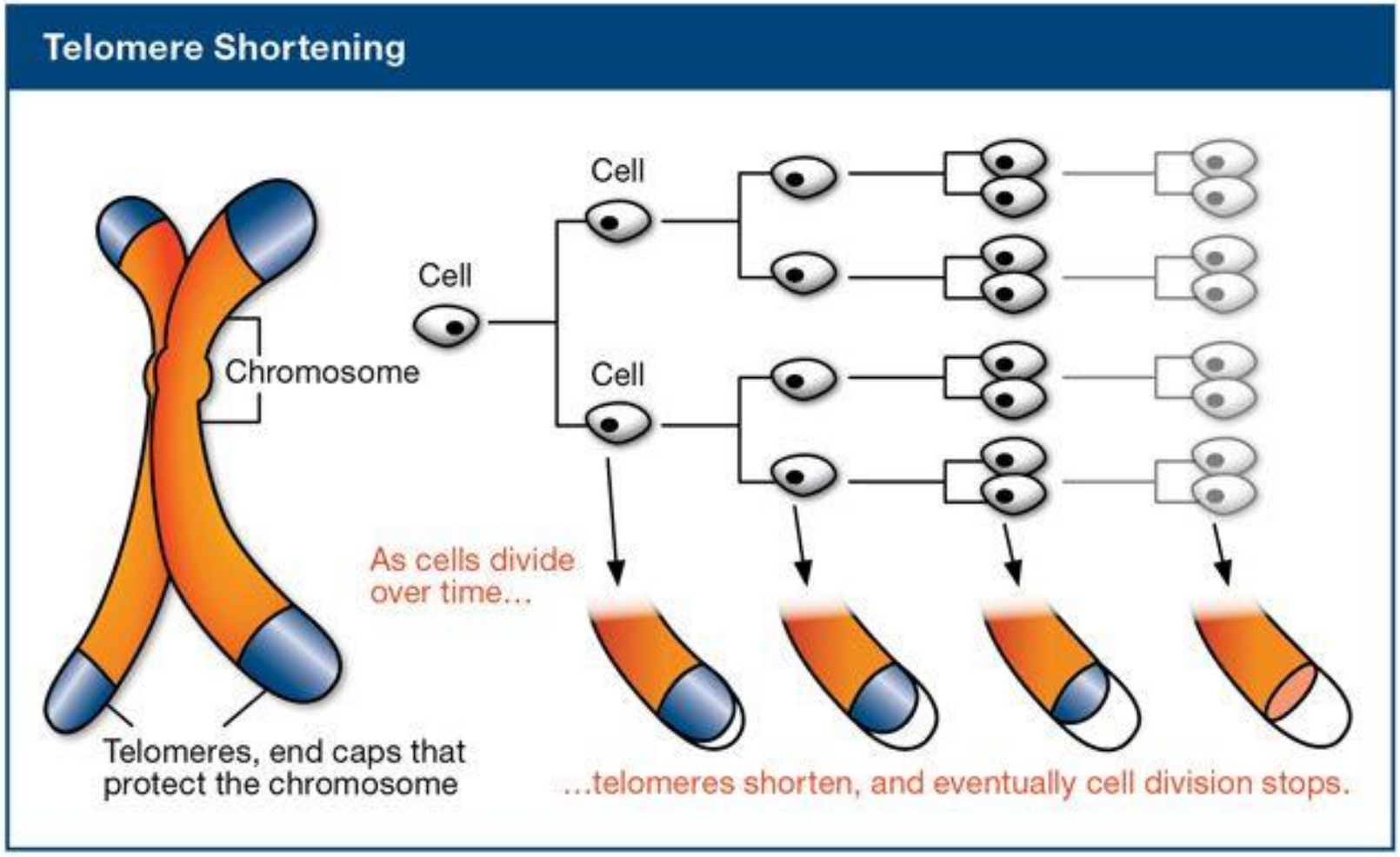
Telomere

- Telomeres shorten in part because of the end replication problem that is exhibited during DNA replication in eukaryotes only.
- On the leading strand, DNA polymerase can make a complementary DNA strand without any difficulty .
- At the end of lagging strand where the last RNA primer has no place to attach on other end a section of the telomere is lost.

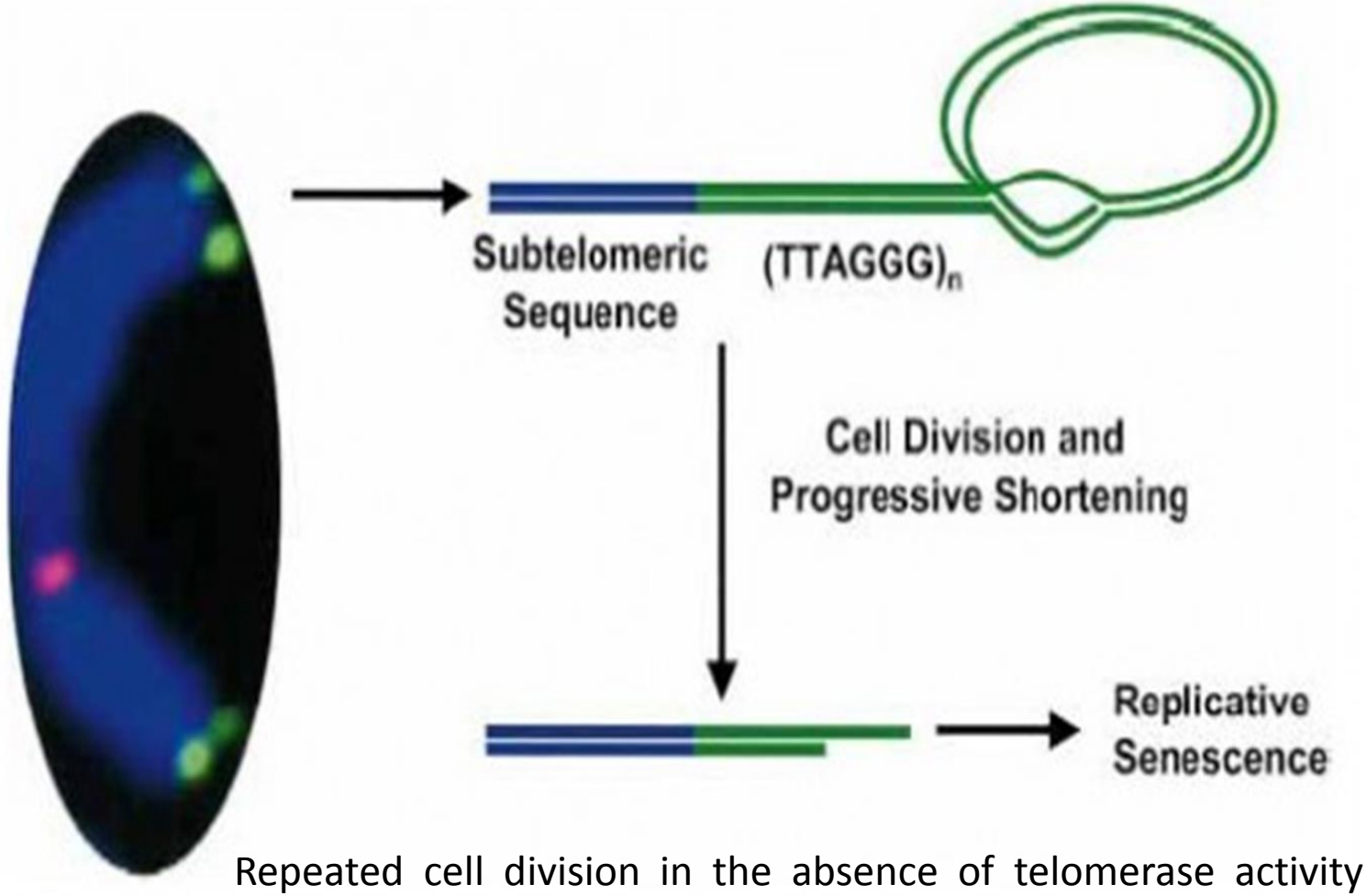
Telomere


Lagging strand
DNA synthesis
RNA primer
Parent strands
3'
5'
Leading strand
DNA synthesis
Chromosome end
3'
5'
Polymerase
Primer
3'
5'
3'
Ligation
Gap fill-in
Primer
removal
3'
5'
3'
5'
Shortened end
Gap cannot be filled because
primer has no place to attach on
the other end.
3'
5'

Telomere

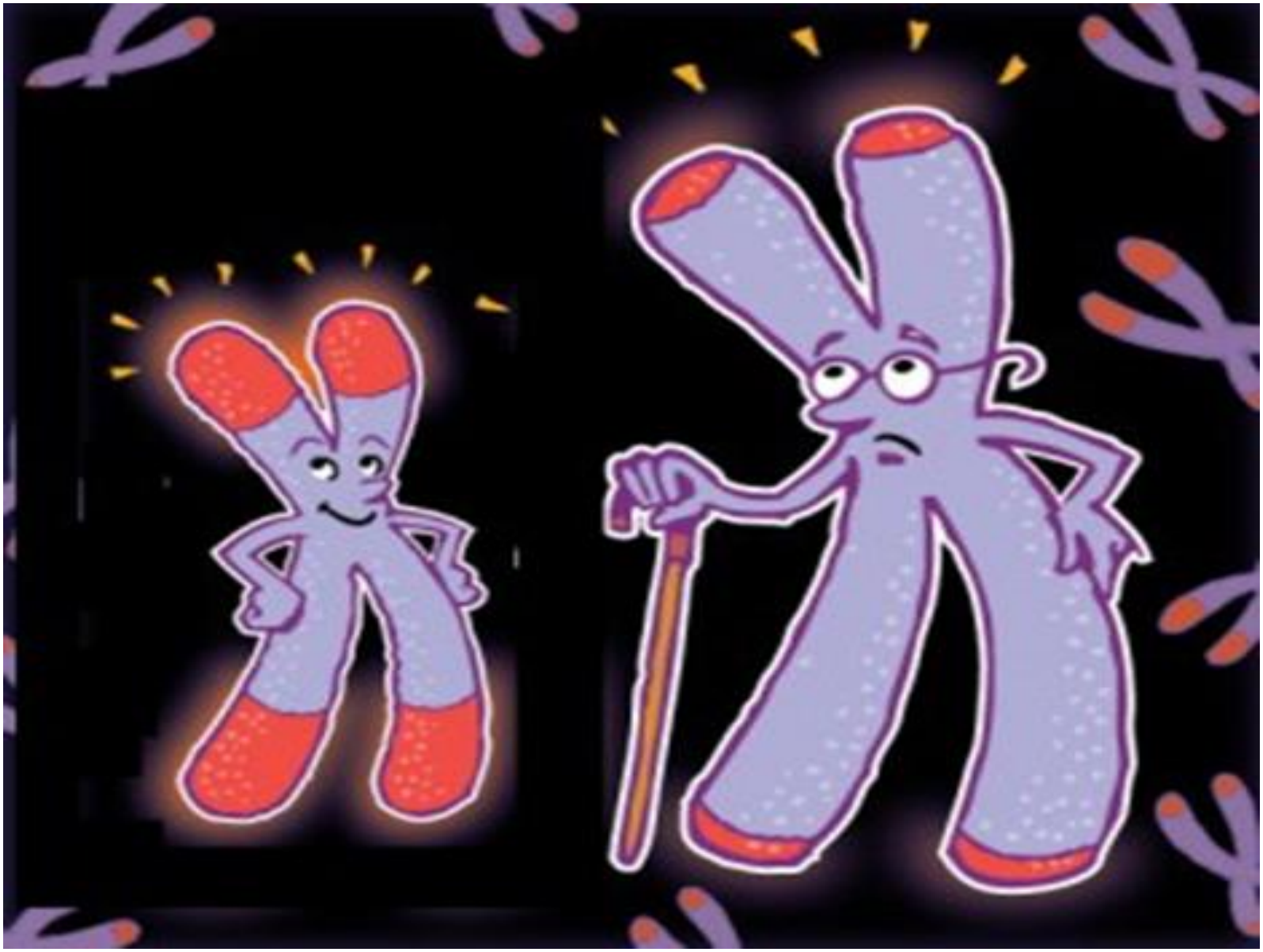

Telomere Shortening
Cell
Cell
Cell
Chromosome
As cells divide over time...
Telomeres, end caps that protect the chromosome
...telomeres shorten, and eventually cell division stops.

Telomere



Repeated cell division in the absence of telomerase activity leads to telomere shortening and replicative aging. Telomerase enzyme, capable of increasing telomeres after shortening, is not active in most somatic cells.

Telomere

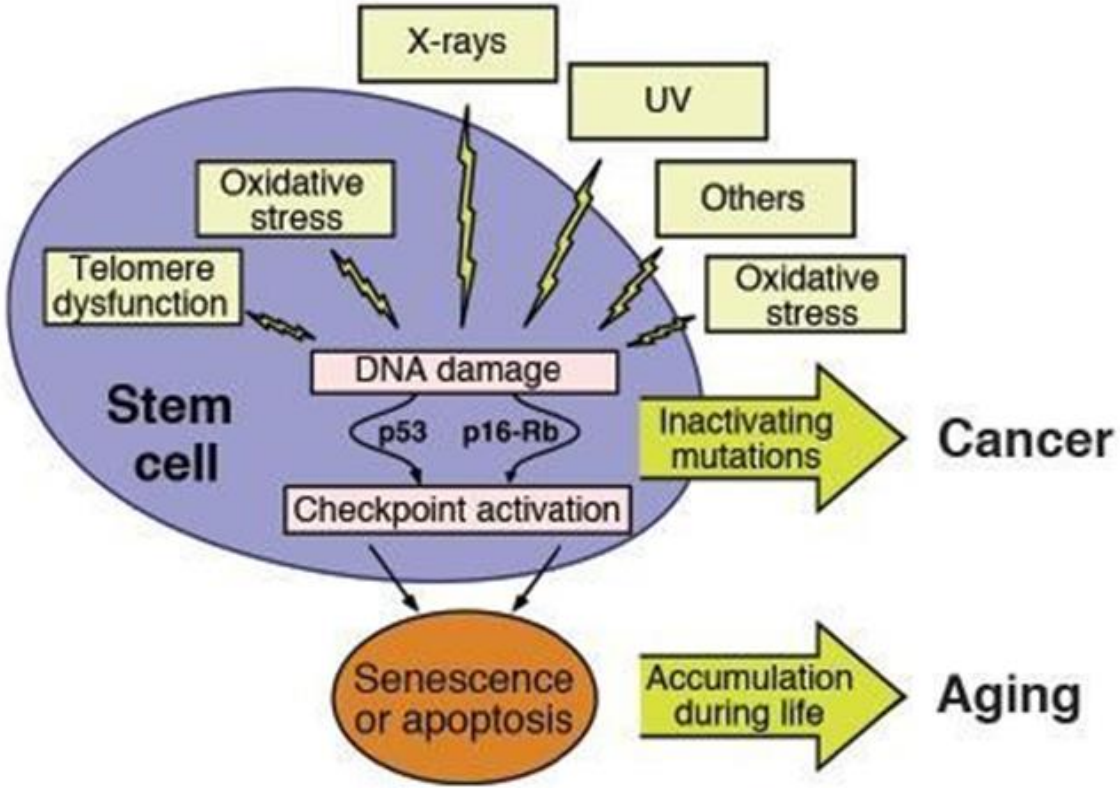


Molecular mechanisms of replicative aging

- The process of cell division is called proliferation. The time of cell existence from division to division is called the cell cycle.
- The cell cycle is regulated by cyclin-dependent kinases which is different for each stage of the cell cycle. They are activated by cyclins and inactivated by a number of inhibitors. The purpose of such a complex regulation is to provide DNA synthesis with as few errors as possible so that the daughter cells have absolutely identical hereditary material.
- Verification of DNA copying is carried out at “control points” of the cycle: if errors are detected, the cell cycle is stopped and DNA repair is turned on. If the violation of the DNA structure can be corrected - the cell cycle continues. If not, it is better for the cell to “commit suicide” (through apoptosis) in order to avoid the possibility of becoming cancer.

Molecular mechanisms of replicative aging

Molecular mechanisms leading to irreversible cell cycle arrest are controlled by tumor suppressor genes, including p53 and pRB, associated with inhibitors of cyclin-dependent kinases.



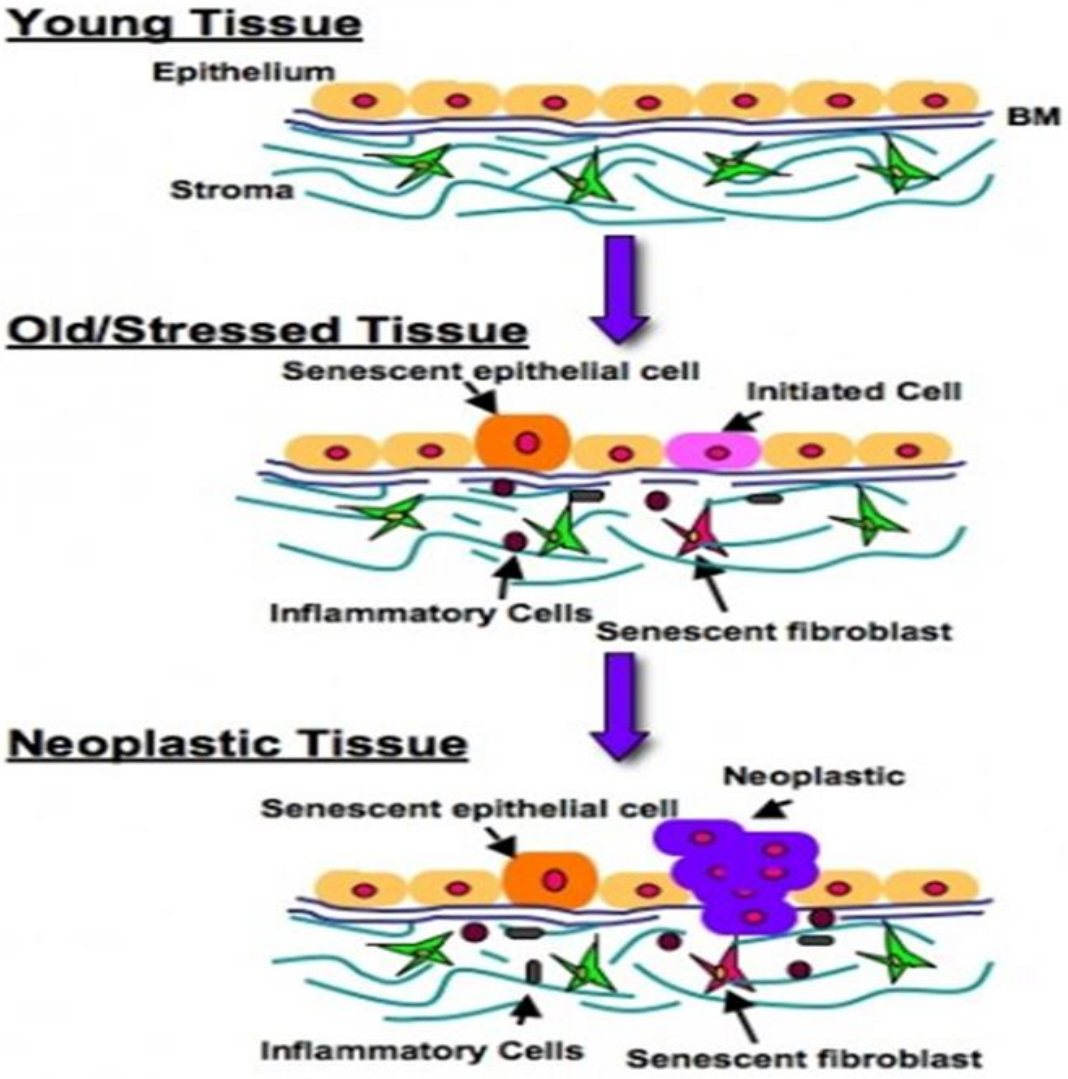
Relationship between cell aging and organism aging

- In the past years, molecular mechanisms of cell aging, their connection with cancer and inflammation have been discovered.
- According to modern concepts, inflammation plays a leading role in the genesis of almost all age-related diseases, which ultimately lead to the death of the body.

Relationship between cell aging and organism aging

Old cells are resistant to apoptosis, which suggests that they can accumulate throughout the life of the organism. The actual rate of accumulation of old cells in vivo is not known. Since each cell in the body is surrounded by other cells that interact with each other, changes in the secretory profile of old cells change the tissue microenvironment and affect the functions of neighbour cells. In addition, cell aging decreases the ability of tissues to self-renew (by influencing neighbour cells through secretory molecules).

Relationship between cell aging and organism aging



Replicative aging and premature aging

Causes of premature aging:

1.Decrease in cell proliferative potential;

2.Epigenetic mechanisms, such as DNA methylation (DNA methylation reduced), post-transcriptional modifications of core histones and dynamic transformations of chromatin;

3. Decrease in the level of HP1 (Heterochromatin protein 1);

4. Effect of free radicals on a cell;

5.Influence on the body of various environmental factors and/or improper lifestyle;

6.Genetically determined forms of premature aging which due to mutations of specific genes

Progeria

- Progeria is an extremely rare genetic disorder which associated with premature aging.
- The two major types of progeria are Hutchinson-Gilford progeria syndrome (HGPS), which has its onset in early childhood, and Werner syndrome (adult progeria), which occurs later in life.

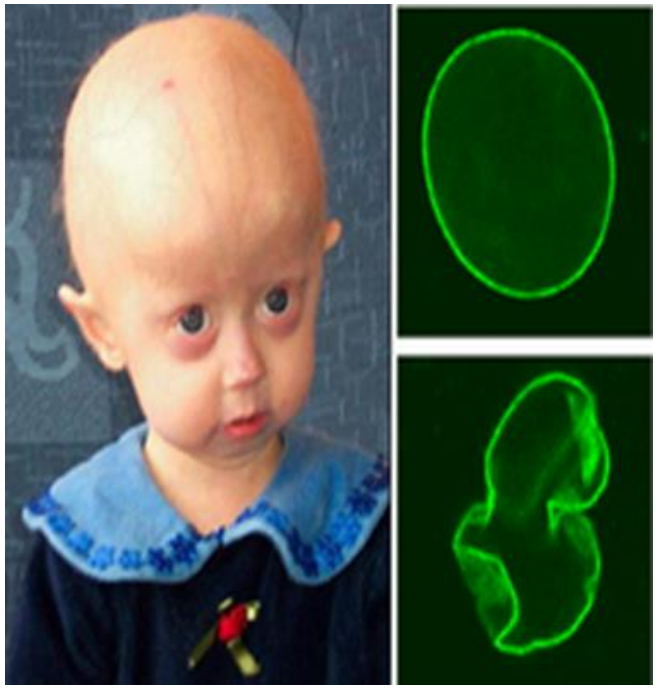
Progeria

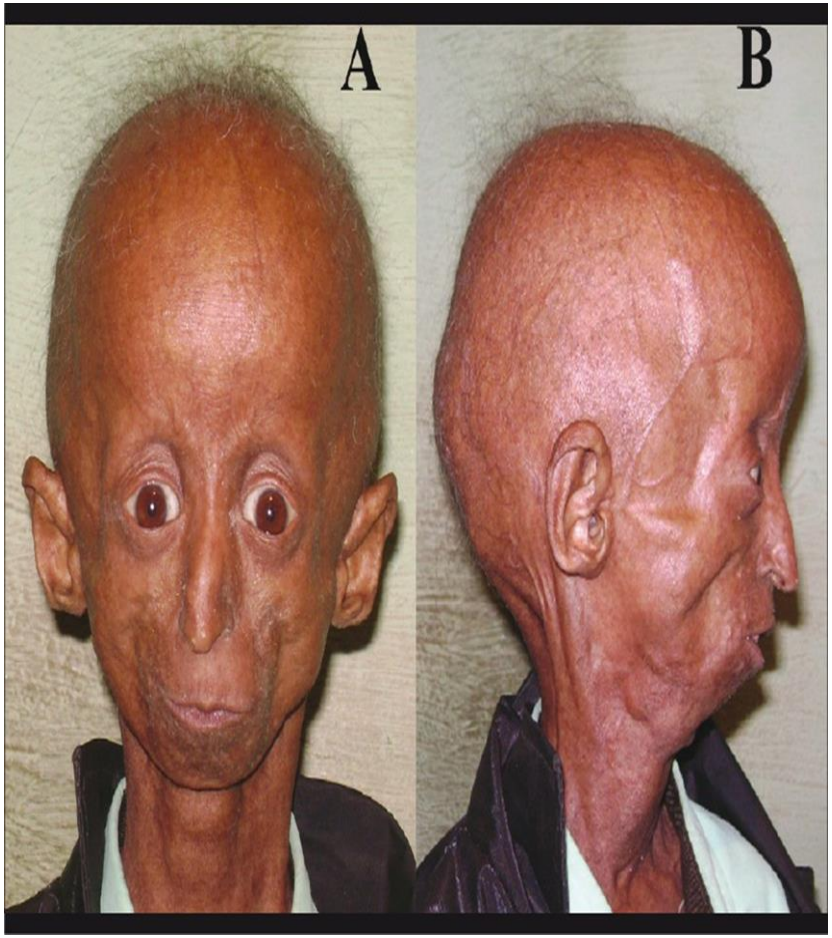
- The cause of **Hutchinson-Gilford progeria** (child progeria) is a mutation of the LMNA gene encoding lamin A that weaken the structure of the cell nucleus, making normal cell division difficult. Lamines are proteins that make up a special layer of the membrane of the cell nucleus.

Progeria

- Signs of **Hutchinson-Gilford progeria** syndrome appear at about age one, after an evidently normal infancy. Affected individuals seldom exceed the size of a normal 5-year-old, although they have the physical appearance of 60-year-old adults by the time they are 10.
- Many of the superficial aspects of aging, such as baldness, thinning of the skin, prominence of blood vessels of the scalp, and vascular diseases, occur. Sex organs remain small and underdeveloped. A few individuals with progeria are intellectually disabled, but most have normal intelligence and may even be precocious. By age 10, extensive arteriosclerosis and heart disease have developed, and most patients die before they reach 30; the median age of death is 13. The condition is not inherited.

Hutchinson–Gilford progeria





Progeria

- **Werner syndrome** (adult progeria) has an autosomal recessive type of inheritance. Defective gene - WRN (ATP-dependent helicase gene). It is assumed that the process is associated with a violation of DNA repair, connective tissue exchange.

Progeria

Werner syndrome typically appears following puberty, with visible signs of aging becoming most apparent after age 20.

The aging changes are such that affected persons look about 30 years older than their chronological age. Individuals may not attain their projected adult height, since the growth spurt of adolescence may be blunted.

Patients with Werner syndrome are sexually mature, but secondary sex characteristics are poorly developed. Superficial signs of aging are premature balding or graying of hair, loss of teeth and hearing, cataracts, acute arthritic episodes, skin ulcers, and osteoporosis (loss of bony tissue). There is an increased tendency to develop heart disease, diabetes mellitus, and cancer, and the average life span is 47 years.

Werner syndrome

- The atrophy of the muscles of the arms and legs begins to progress, the fatty tissue, arms and legs gradually begin to become excessively thin and disproportionate, there is a sharp restriction of their mobility.
- There are noticeable changes in facial features - the chin begins to come forward significantly, all features become sharp and pointed outlines, the nose in its shape begins to look like a sharp bird's beak, along with these changes, the size of the mouth decreases.

Werner syndrome

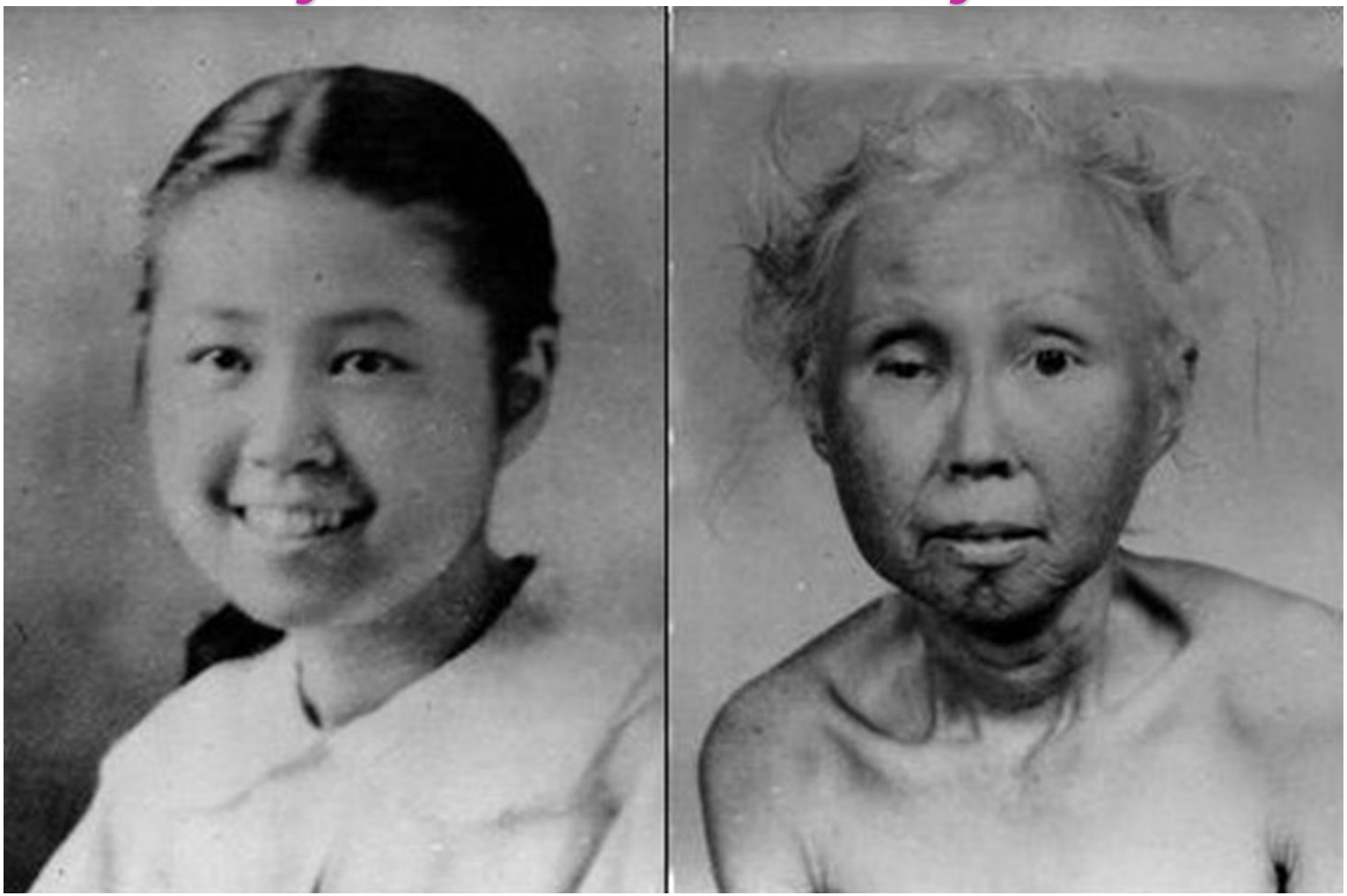
14 years

23 years

Werner syndrome

Werner syndrome

15 years 48 years



Werner syndrome

19 years

32 years

Werner syndrome

24 years 39 years

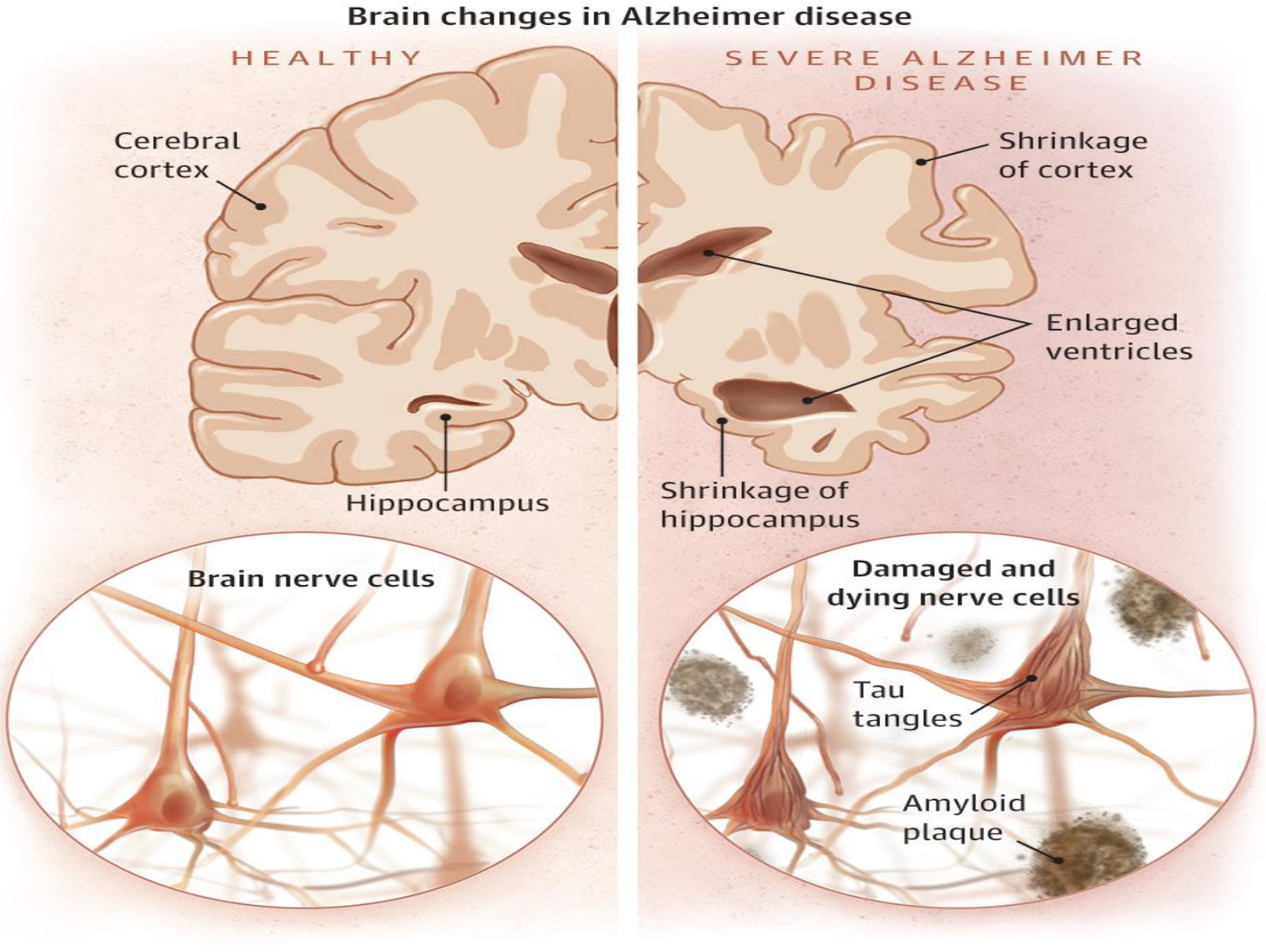
Dementia

- Dementia is a term used to describe a general decline in all areas of mental ability. Traditionally, dementia was divided into ‘presenile’ or ‘senile’.
- Presenile dementia has an onset before 65 years of age.
- Senile dementia has an onset after 65 years of age.

Alzheimer's disease

- Alzheimer's disease is the most common degenerative dementia. Alzheimer's disease most commonly occurs in late life, but a small percentage of patients have onset before 60 years (presenile).
- Initial symptoms are often mistaken for normal aging. Examination of brain tissue is needed for a definite diagnosis.
- Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions.

Alzheimer's disease



Alzheimer's disease

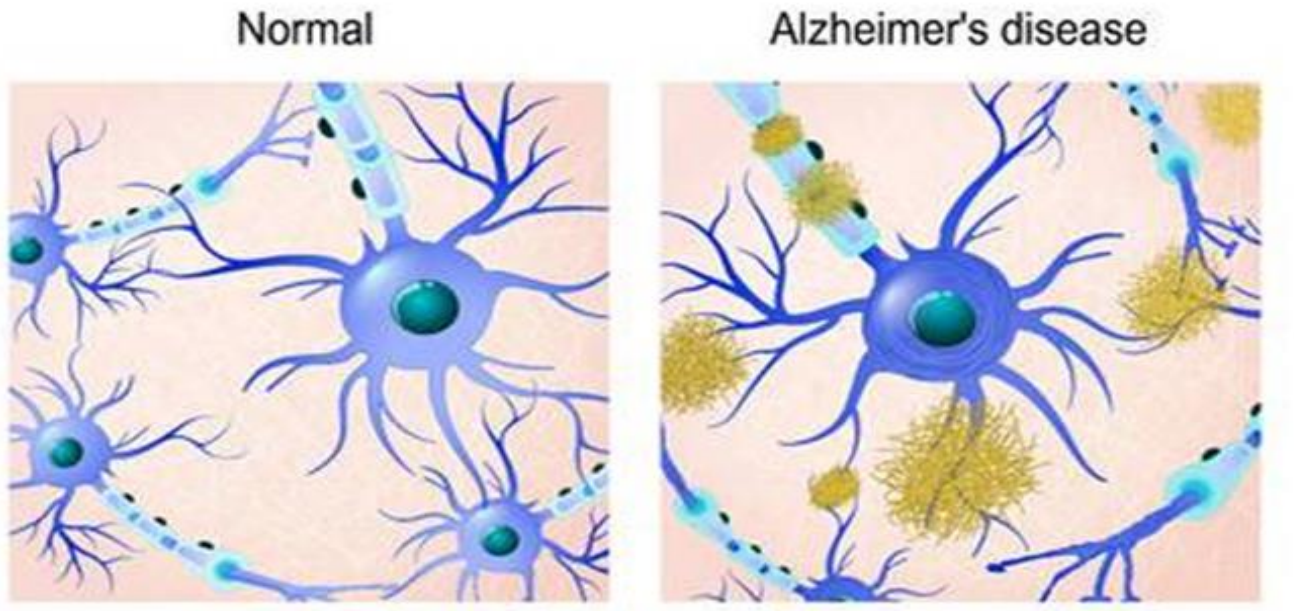
- With the development of the disease, there is a loss of long-term memory, there are impaired speech and cognitive functions, the ability to navigate in the environment and care for yourself is lost.
- The gradual loss of body functions leads to death.

Alzheimer's disease

- **Early-onset Alzheimer's**. This type happens to people who are younger than age 65. Often, they're in their 40s or 50s when they're diagnosed with the disease. It's rare - up to 5% of all people with Alzheimer's have early-onset. People with Down syndrome have a higher risk for it. Scientists have found a few ways in which early-onset Alzheimer's is different from other types of the disease. People who have it tend to have more of the brain changes that are linked with Alzheimer's. The early-onset form also appears to be linked with a defect in a specific part of a person's DNA: chromosome 14. A form of muscle twitching and spasm, called myoclonus, is also more common in early-onset Alzheimer's.
- **Late-onset Alzheimer's**. This is the most common form of the disease, which happens to people age 65 and older.
- **Familial Alzheimer's disease (FAD**) is a form of Alzheimer's disease that doctors know for certain is linked to genes. In families that are affected, members of at least two generations have had the disease. FAD makes up less than 1% of all cases of Alzheimer's. Most people who have early onset Alzheimer's have FAD.

Alzheimer's disease

- Neurons in the healthy brain and Alzheimer's disease with amyloid plaques (misfolded proteins).



Cockayne syndrome

- Cockayne syndrome is a rare autosomal recessive premature aging disease. There are three subtypes of this symptom:
- Cockayne syndrome type 1 (type A), sometimes called “classic” or "moderate" Cockayne syndrome, diagnosed during early childhood
- Cockayne syndrome type 2 (type B), sometimes referred to as the “severe” or "early-onset" type, presenting with growth and developmental abnormalities at birth
- Cockayne syndrome type 3 (type C), a milder form of the disorder
- Cockayne syndrome is caused by mutations in either the ERCC8 (CSA) or ERCC6 (CSB) genes.

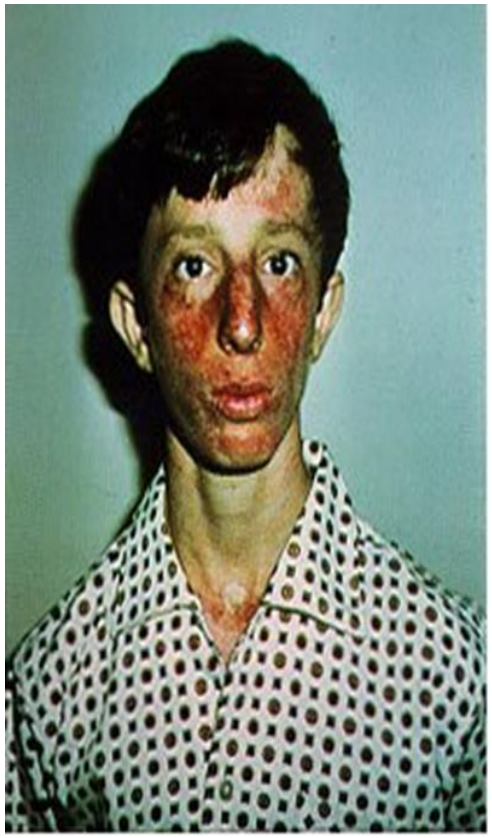
Cockayne syndrome

Bloom syndrome

- Bloom syndrome (BS) is a very rare autosomal recessive disorder.
- BS is caused by mutations in the BLM gene leading to mutated DNA helicase protein formation. Cells from a person with Bloom syndrome exhibit a striking genomic instability that includes excessive crossovers between homologous chromosomes and sister chromatid exchanges (SCEs). The average life span is approximately 27 years.

Symptoms:

- short stature;
- sun-sensitive skin changes on the face, hands and/or arms;
- a high-pitched voice;
- distinctive facial features including a long, narrow face, small lower jaw, large nose and prominent ears.
- learning disabilities;
- an increased risk of diabetes;
- chronic obstructive pulmonary disease (COPD);
- recurrent infections of the upper respiratory tract, ears, and lungs during infancy.
- Cancers may include any of those found in the general population, but develop much earlier in life in affected individuals.



Dependence of aging on the genotype

There are several mechanisms for the genetic control of aging processes.

- Firstly, it is a pleiotropic effect, peculiar to many genes.
- Secondly, over time, mutations accumulate in the genes of somatic cells, the consequences of which are increasing violations of the intracellular mechanisms, processes of replication, reparation, and transcription of DNA.
- Thirdly, genetic predisposition to chronic diseases can influence the rate of aging: hypertension, coronary heart disease, atherosclerosis of cerebral vessels inherited in a polygenic type.

Longevity

- **Longevity** is a socio-biological phenomenon, characterized by human survival to high age limits, significantly exceeding the average life expectancy. Long-liver is a person older than 90 years.
- You may think that your genes determine your longevity, but the truth is genetics account for a maximum of 30% of your life expectancy. The rest comes from your behaviors, attitudes, environment, and a little bit of luck. Although over 200 gene variants have been associated with longevity according to a US-Belgian-UK research database of human genetic variants, these explain only a small fraction of the heritability.

Longevity

- Various factors contribute to human longevity. The maximum lifespan is determined by the norms of aging, a congenital predisposition, depending on the genes (“Mafusail's genes”) and external environmental factors. The main significant factors that affect a person’s life expectancy include sex, heredity, accessible level of health and hygiene, diet and food quality, level of physical activity, lifestyle, social environment, level of consumption. Average life expectancy (and therefore the number of long-lived people, long-livers) differs from country to country.

Clinical and biological death

Clinical death is a reversible stage of death, a transitional period between life and biological death. At this stage, the activity of the heart and the process of respiration cease, all external signs of the vital activity of the organism completely disappear. At the same time, hypoxia (oxygen starvation) does not cause irreversible changes in the organs and systems most sensitive to it. This period of the terminal state, with the exception of rare and casuistic cases, on average lasts no more than 3-4 minutes, a maximum of 5-6 minutes.

Clinical and biological death

- **Biological death** (or true death) is an irreversible cessation of physiological processes in cells and tissues.
- Signs of death are:
  - Respiratory arrest (no breathing)
  - Cardiac arrest (no pulse)
  - Brain death (no neuronal activity)
  - Paleness which happens in the 15–120 minutes after death
  - Reduction in body temperature
  - limbs of the corpse become stiff (Latin rigor) and difficult to move or manipulate
  - settling of the blood in the lower (dependent) portion of the body


'THANK YOU'