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Biology in Search of the Elixir of Youth

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Since the dawn of existence, humans have sought to defy the inevitability of death. This struggle gave rise to religions that dominated human culture for centuries and was crucial to philosophies shaping our civilizations. But is it possible that a scientific solution for achieving immortality is finally within reach? In recent years, artificial intelligence (AI) has reached a stage where it seems ready to revolutionize every aspect of our lives. Perhaps this will change the way we think about—perhaps even experience—death. Will humanity exist without biological embodiment in the near future? Can humans and artificial intelligence merge into a single existence?

Meanwhile, visionaries in the field of geroscience (the modern approach of study of aging and longevity), such as Aubrey de Grey, predict that advancements in medical technology (not necessarily AI) will soon extend human life to lengths approaching thousands of years. Aubrey de Grey was once relatively isolated in his predictions, but lately, the voices of other scientists advocating for significant life extension have grown stronger. While achieving eternal youth and Methuselah-like ages might not be guaranteed, living in health up to its maximum limit, as demonstrated by Ms. Calmont's over 122 years of life, seems plausible. In this context, the contribution of AI is not insignificant, as it can aid in the effective discovery of a drug that significantly extends life and delays aging. It appears that, to

some extent, aging can be treated. The concept of geroscience assumes that the same cellular and molecular mechanisms underlie both age-related diseases and the biological aging process. By influencing these mechanisms, we can not only cure age-related diseases but also significantly delay aging. With help in “treatment” old age comes approved at the beginning 2022 by WHO, and implemented by all Member States, new classification system ICD-11 drugs (International Classification of Diseases ICD-11 system). In this classification so far “old age” in the “General” category “Symptoms” was replaced by the term: “Aging-associated decline in intrinsic capacity”, i.e. “related with aging, a decline in inner capabilities.” Moreover, there are approximately fourteen ‘matches’ terms” to this code referred to as MG2A, including “senile frailty”, “senile atrophy”, “senile exhaustion”, “senile weakness”, and also “aging” itself. All these terms allow to directly define aging as a medical condition or set of general symptoms medical! So, aging is treatable. The assistance of AI is crucial in this, as it can contribute to the efficient discovery of an effective life-extending drug. It seems that aging can be treated to some extent.

Not too long ago, an anti-aging drug would have been considered pure heresy because old age was seen as a normal stage in our physiological existence. A quarter of a century ago, scientists believed that physiological aging, exemplified by individuals

living to a hundred or more years (so-called successful aging), could be distinguished from pathological aging, burdened with numerous diseases of old age and premature death, preventing the attainment of such advanced ages. Currently, old age can be treated as a disease, and, most importantly, drugs alleviating the symptoms of aging, not just specific diseases associated with aging, such as neurodegenerative diseases, cardiovascular diseases, bone and joint diseases, and metabolic diseases like type II diabetes, can be tested in clinical trials. However, a significant problem arises here. Although we know many aging mechanisms, often referred to as aging markers, paradoxically, it is still challenging to determine what a potential anti-aging drug can change if it cannot be described as a modification of disease symptoms. Yet, in recent decades, science has begun to provide solutions in this regard. Biological clocks have been described that objectively determine biological age. Unlike chronological age, we can unconsciously and consciously influence biological age, either accelerating or decelerating the biological clock. Biological clocks, including the most developed epigenetic clocks, do not directly refer to diseases but to biological processes. In this case, these are chemical modifications of DNA and proteins building chromatin. The good news is that not only drugs but also nutraceuticals (natural substances with therapeutic effects) and a proper lifestyle, including diet, physical activity, avoiding excessive stress, and ensuring good sleep and intellectual and social activity, influence these chemical modifications. Methylation of DNA, well-described and relatively easy to measure, especially in peripheral tissues such as blood, is among the best-described modifications.

Chromatin is located in the nucleus, which generally occupies a central place in every cell. Cells, in turn, are the basic building blocks of our body's tissues. Over time, the body accumulates cells with many unrepaired damages, including organelles such as mitochondria as well as macromolecules, such as proteins and DNA. Cells in which self-repair mechanisms, recycling (autophagy), divisions, and death fail, and whose entire life energy is directed towards secretory activity are senescent cells. Factors like growth factors, pro-inflammatory cytokines, small RNA (microRNA), enzymes, and various proteins are released from these senescent cells into the environment, causing havoc in the body by spreading the aging process and a low-intensity chronic inflammatory state with very serious consequences in the form of age-related diseases. Aging not only affects cells in many tissues but also, so-called inflammaging, along with the aging

of immune cells (immunosenescence), makes our body more susceptible to diseases and less susceptible to vaccinations, although the intensity of these processes is highly individualized. Anti-aging drugs increasingly target senescent cells, and their elimination or at least reduction is expected to improve physical fitness and cognitive abilities. As senescent cells also have positive effects, such as stopping the transformation into cancer, or aiding in wound healing, senotherapy, which is targeting senescent cells, may involve their secretory capabilities rather than the elimination of entire cells. Interestingly, inducing aging in cancer cells through radio/chemotherapy leads to unfavorable outcomes, as senescent cancer cells, after a period of halted divisions, can acquire characteristics of highly invasive cancer cells.

The aging process affects all systems of the body. The skin, which is most visibly affected, ages due to endogenous processes and exposure to adverse environmental factors. Although wrinkles don't cause death, they represent a tangible effect of undesired passage of time and environmental influences (sun), often impacting well-being. In this case, the development of aesthetic medicine offers hope for restoring a youthful appearance. Increasingly available techniques can take a few or several steps to rejuvenate our skin by even several years. While the skin ages "before our eyes," the aging of the female reproductive system is mainly observed through its effects. The occurrence of menopause in women and some animals remains a continuous puzzle. However, it seems that cellular senescence may play a non-negligible role in this process, and senotherapy may be a solution for late motherhood. Similarly, it appears that senotherapy can not only delay and alleviate the symptoms of dementia but also positively affect cognitive abilities, which tend to decline with age.

Living at the turn of the 19th and 20th centuries, Ilja Miecznikov believed that yogurt was the true elixir of youth. It is not a recent discovery that the composition of food provides the body with not only building blocks, energy, vitamins, and enzymes necessary for functioning but also affects signaling pathways that are constantly activated or inhibited, ensuring the proper functioning of this incredibly complex machinery that is the body. Interestingly, an integral part of it is the microbiome. About a kilogram of bacteria inhabiting our intestines, and not only, ensures the proper functioning not only of the digestive system but also the immune system and the central nervous system. Disturbance of microbiome homeostasis disrupts the body's homeostasis and contributes to its aging. Yogurt, rich in probiotics, will not restore the young composition of our

microbiota, but it can certainly alleviate the symptoms of its changes accompanying the aging of the body. Similarly, physical activity and a proper diet seem to have an impact. It also seems that senolytics have a “rejuvenating” effect on the microbiome.

“The Miracle Diet” is almost every person’s dream who struggles with excess weight. It seems that caloric restriction, meaning the daily reduction of calories without causing nutritional deficiencies, can be such a diet. As a result of calorie restrictions, not only do we lose kilograms, but we also give ourselves a chance for a longer and healthier life. However, the costs of this can be very high in the form of apathy, decreased libido, and a withdrawal from social life. Therefore, a significant hope for the obese, whose expected lifespan is lower than average, may be mimetics of a low-calorie diet. These include metformin, rapamycin, or resveratrol. They strongly intervene in metabolism, and their use as anti-aging drugs has its limitations.

Currently, we are witnessing a trend towards longevity. The generation of 30 to 40-year-olds is actively seeking ways to extend life. They invest their time and money in physical activity, proper nutrition, and aesthetic medicine. Longevity clinics are emerging, where individuals can determine their biological age, identify any deficiencies, and undertake personalized actions aimed at reducing their biological age. For now, this is a way to longevity for the wealthy, much like taking numerous substances daily to maintain youthful vigor. The market offers us an endless number of “anti-aging” substances. However, taking all of them is not only expensive but also seems impractical. There is no guarantee

that these substances will work additively. There are still few studies on the synergistic effects of nutraceuticals. Therefore, individuals who wish to live healthily and long should carefully follow the progress of scientific research and be open to their critical perspective. The monograph “Biology in Search of the Elixir of Youth” does not cover all aspects of these studies, but we hope it serves as a good starting point and encourages authors to share their, sometimes controversial, knowledge with eager readers.

The aging process is multi-faceted and complex. Interestingly, by influencing one element of the organism’s aging, such as the epigenome, microbiome, or senescent cells, a global rejuvenating effect can be achieved. Remember this, dear reader, when you read chapters addressing various aspects of aging in this edition. Everything is connected. Moving a small stone can trigger an avalanche of beneficial processes. In an era of increasing awareness of people about real possibilities to counteract aging, often through actions that do not require large economic investments but require sound knowledge, we present you with this monograph. We hope it enriches your knowledge on aging and longevity in an accessible way. We also hope that this issue will encourage young biology and medicine enthusiasts to engage in this issue professionally, contributing to the development of geroscience and preserving humanity in its full biological dimension.

Happy reading!



