CAN'T WE STAY YOUNG FOREVER?

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Introduction

Editorial

For centuries, explorers and travellers have devoted years of their lives in search of the Fountain of Youth: a source which, if bathed in or drunk from, would provide you with eternal youth and longevity. There are some indications of the existence of such a source, but they have never been confirmed; the fountain is widely seen as a myth. The wish for eternal life, however, remains. Could it, with the current or future technology and knowledge, be possible to fulfill this wish?

Death is inevitable. Right? This is not necessarily true, according to biomedical gerontologist and Chief Science Officer and Co-founder of the SENS Research Foundation Aubrey de Grey. He perceives ageing as a disease that can be cured and believes that we will be able to defeat ageing and thus prolong life - indefinitely. His main argument for why we should cure ageing is because it kills people. Before being able to find possible therapies that could prevent or reverse ageing and age associated diseases, we need to know what exactly ageing is.

Ageing is often defined as "the process of growing old" or "relating to getting older" [1, 2]. However, it can also be defined as all changes that occur with the passage of time in a (human) body including growth and differentiation, which can result in an increased probability of death as someone grows older [3]. It is suspected that an accumulation of damage is responsible for the symptoms of ageing and there are several theories about this [3, 4]. The process of ageing results in a loss of cells and therefore loss of (organ) function and increased vulnerability [3]. Some of the theories on the process of ageing are more plausible than others. Nonetheless, all of them are considered possibilities and no consensus on which one is true has been reached. The Programmed theory exists of three subcategories: the Programmed Longevity, the Endocrine theory and the Immunological theory. The Programmed Longevity states that ageing is programmed genetically, which means that it is essentially the last step in development. The Endocrine theory suggests that hormones are responsible for the pace of ageing. Finally, the Immunological theory proposes that the immune system is programmed to decline over time, which leads to increased susceptibility to infectious diseases and ageing and death. Other theories, e.g. the War and Tear theory, which says that cells and tissues wear out due to repeated use, or the Free Radicals theory, which hypothesises the fact that radicals such as reactive oxygen species (ROS) cause cellular and DNA damage, exist as well. [3, 4] The Somatic DNA Damage theory, in which DNA damage is responsible for deterioration and malfunction of cells due to DNA repair defects is also imaginable. Perhaps the best known is the Telomere theory. The shortening of the telomeres with each cell division can cause genomic instability and is associated with ageing. As mentioned before, there is no consensus on which theory is the correct one, and it is highly probable that the truth consists of a combination of the many theories.

Beside this, Aubrey de Grey proposes seven types of damage [5, 6] that have been established that lead to ageing: (i) cell loss or atrophy; (ii) cell senescence, which is the irreversible cell cycle arrest [7]; (iii) nuclear (epi) mutations or cancerous cells; (iv) mitochondrial mutations; (v) protein crosslinks; (vi) extracellular aggregates; and (vii) intracellular aggregates [5, 6]. As you grow older, tissue-specific stem cells become less effective in replacing damaged or dead cells, meaning that long-lived tissues will lose cells and the function of a damaged organ will be compromised. This results in weakening of muscles, loss of neurons, leading to cognitive decline [8]. Senescent cells are cells that have lost the ability to divide, e.g. when abnormal changes in DNA expression are observed. However, these senescent cells are alive and can still produce proteins and secrete them, eventually causing inflammation, which causes damage. Mutations and epimutations also induce damage by causing abnormal gene expression, changing the conditions in which the protein is expressed or by altering the protein structure and thus the function. These can all lead to cancerous cells and uncontrolled growth.

Premature ageing syndromes

It is also possible to gain insight into the ageing process by looking at premature ageing syndromes, which are diseases that cause ageing symptoms at a very early age. Examples of these are the Werner syndrome (WS) and the Hutchinson-Gilford progeria syndrome (HGPS). WS is a rare autosomal recessive disorder and patients have a life expectancy of 47 to 54 years. The ageing symptoms can start to occur when the patients are in their teenage years and resemble many signs of normal ageing, including grey hair, cataracts, ischemic heart disease and osteoporosis [9, 10]. The cause is often a mutation in the *WRN* gene that codes for the Werner protein, which is important for DNA replication and repair and telomere maintenance. The mutation often leads to a shortened protein that is unable to be transported to the nucleus, where it normally executes its function [9-11]. Cells from individuals with WS present themselves with increased chromosomal aberrations, premature cell senescence in vitro and accelerated telomere shortening. HPGS is a slightly more severe disease. Children seem healthy at birth, but develop clinical symptoms soon thereafter, including for example growth failure. A remarkable aspect is that patients retain normal cognitive function and development. Life expectancy ranges from 8 to 21 years and death is often caused by a stroke or cardiovascular disease [9, 10]. Since patients often do not live to a reproductive age, the mutation responsible for HGPS is rarely inherited. Often the cause is an autosomal dominant de novo point mutation in the *LMNA* gene [9, 10], leading to a mutant lamin protein, normally situated in the inner nuclear lamina that is involved in many nuclear activities as DNA replication, nuclear migration, cell development and apoptosis [12]. There is no cure available for either WS or HPGS and the only option is to treat symptoms [9]. Based on these observations, one may conclude that genetic components are involved in ageing. In the case of these two syndromes, a mutation is responsible for accelerated ageing, but could the opposite be true as well?

Genetic components in longevity

Researchers from the University of California have found mutations in the *daf-2* gene of the *C. elegans*, causing them to live an active life for twice

as long as as the wild type [13]. This gene codes for a hormone receptor. Due to the mutation, the receptor's function is reduced. The same effect has been observed in flies and mice [14, 15]. The human equivalent of the *daf-2* receptor is the insulin and insulin-like growth factor 1 (IGF-1) receptor. The IGF signaling pathway has also been suggested to have an effect on the human lifespan [16, 17]. In research of Suh et al. (2008) [16], mutations in the IGF-1 receptor (IGF1R) gene were more prevalent in female centenarians compared to controls. These mutations were associated with reduced IGF1R activity and higher serum IGF-1 level as a compensatory method. Later, an association between IGF-1 serum levels and survival was observed [17]. Here, low IGF-1 levels were correlated with a higher survival in females, especially in individuals with a history of malignancy. Overall, some individuals may experience benefits from certain genetic variations, resulting in a prolonged life.

Slowing or reversing ageing

Other researchers are working on unraveling possible solutions for ageing. At the SENS Research Foundation, researchers are exploring several possible therapies for slowing ageing, like cell therapy and tissue engineering. However, what may be even more interesting, is that some researchers are looking at a way to reverse ageing and actually believe the Fountain of Youth may be within us. In an animal study, a young mouse's blood circulation was connected to that of an aged mouse through parabiosis and it was found that the exposure of the old mouse to the young mouse's blood improved stem cell function in muscles, liver and the brain. In another study, aged mice (18 months old) were either given an intravenous injection of "young" plasma, from 3 month old mice, "aged" plasma, from 18 month old mice, or no injection. Aged mice given young plasma showed enhanced learning and memory compared to the aged mice given old plasma or untreated mice [18]. This study shows that exposure to young blood may enhance cognitive function in aged mice, but also counteract ageing at a molecular and structural level. This suggests that young blood may contain factors that can reverse ageing or that old blood contains factors that are pro-ageing. Abolishing these pro-ageing factors might counteract ageing. Following these results, a clinical trial was started in Alzheimer patients [19] to assess the effect of regular plasma injections, voluntarily obtained from young men. Even though another study suggests that not the young blood is rejuvenative but perhaps the old blood toxic [20], the implications of certain factors in the blood that can influence ageing are considerable.

Conclusion

Researchers have come a long way in deciphering the mysteries of ageing, but they still have a long way to go. Ageing is a multifaceted issue which means that finding a simple solution is not that straightforward. Besides this, much of the research has been done in vitro or in animals and the techniques that are being used, like genetic engineering of certain age-associated genes, are not ready yet to be applied in humans. Therefore, with the current status of research, we are not yet able to slow, stop or reverse ageing. However, a crucial question remains unanswered: do we want to prolong our lives? Perhaps we should embrace ageing and death as a part of life and consider to stop looking for the Fountain of Youth, because once we have found it, there is no turning back.

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