Immortality Research Literatures

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Abstract: Immortality is eternal life, being exempt from death, unending existence. Some modern species may possess biological immortality. Certain scientists, futurists, and philosophers have theorized about the immortality of the human body, with some suggesting that human immortality may be achievable in the first few decades of the 21st century. Other advocates believe that life extension is a more achievable goal in the short term, with immortality awaiting further research breakthroughs. The absence of aging would provide humans with biological immortality, but not invulnerability to death by disease or physical trauma; although mind uploading could solve that issue if it proved possible. Whether the process of internal endoimmortality is delivered within the upcoming years depends chiefly on research (and in neuron research in the case of endoimmortality through an immortalized cell line) in the former view and perhaps is an awaited goal in the latter case. In religious contexts, immortality is often stated to be one of the promises of God (or other deities) to human beings who show goodness or else follow divine law. What form an unending human life would take, or whether an immaterial soul exists and possesses immortality, has been a major point of focus of religion, as well as the subject of speculation, fantasy, and debate.
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1. Introduction

Immortality is eternal life, being exempt from death, unending existence. Some modern species may possess biological immortality. Certain scientists, futurists, and philosophers have theorized about the immortality of the human body, with some suggesting that human immortality may be achievable in the first few decades of the 21st century. Other advocates believe that life extension is a more achievable goal in the short term, with immortality awaiting further research breakthroughs. The absence of aging would provide humans with biological immortality, but not invulnerability to death by disease or physical trauma; although mind uploading could solve that issue if it proved possible. Whether the process of internal endoimmortality is delivered within the upcoming years depends chiefly on research (and in neuron research in the case of endoimmortality through an immortalized cell line) in the former view and perhaps is an awaited goal in the latter case. In religious contexts, immortality is often stated to be one of the promises of God (or other deities) to human beings who show goodness or else follow divine law. What form an unending human life would take, or whether an immaterial soul exists and possesses immortality, has been a major point of focus of religion, as well as the subject of speculation, fantasy, and debate.

The following introduces recent reports as references in the related studies.

Ahmed, S. (2006). "Uncoupling of pathways that promote postmitotic life span and apoptosis from replicative immortality of Caenorhabditis elegans germ cells." Aging Cell **5**(6): 559-563.

A dichotomy exists between germ and somatic cells in most organisms, such that somatic cell lineages proliferate for a single generation, whereas the germ cell lineage has the capacity to proliferate from one generation to the next, indefinitely. Several theories have been proposed to explain the unlimited replicative life span of germ cells, including the elimination of damaged germ cells by apoptosis or expression of high levels of gene products that prevent aging in somatic cells. These theories were tested in the nematode Caenorhabditis elegans by examining the consequences of eliminating either apoptosis or the daf-16, daf-18 or sir-2.1 genes that promote longevity of postmitotic somatic cells. However, germ cells of strains deficient for these activities displayed an unlimited proliferative capacity. Thus, C. elegans germ cells retain their youthful character via alternative pathways that prevent or eliminate damage that accumulates as a consequence of cell proliferation.

Arlow, J. A. (1982). "Scientific cosmogony, mythology, and immortality." Psychoanal Q **51**(2): 177-195.

Some current scientific theories of cosmogony demonstrate significant similarities to the cosmological theories of mythology and of certain religions. The notion that the universe originated in a specific cataclysmic explosion raises the mental

construct of a center of the universe. This concept plays an important role in mythology and is related to the idea of the cyclical renewal of time. Such concepts, both scientific and mythological, serve as reassurance against the fear of extinction. Aspirations to immortality re-emerge in disguised form in the search for life elsewhere in the universe. Some of the cosmological theories resemble metaphorical elaborations of childhood concepts of procreation.

Arnett, W. S. (1991). "Growing old in the cradle: old age and immortality among the kings of ancient Assyria." Int J Aging Hum Dev **32**(2): 135-141.

The desire for a long and healthy life was expressed often by Assyrian kings in their extant public texts from the 14th through the 7th centuries BC. But advanced old age, whether for monarchs or commoners, was not achieved very often in the ancient world. Consequently, Assyrian royal inscriptions frequently reflect concern for another kind of longevity--an immortality achieved by having one's works and one's name preserved and remembered by posterity. Almost every dedicatory inscription associated with public works--palaces, temples, etc.--expressed the importance of these kings' participation in what this writer terms a "family cult." The latter constituted a sense of continuity from father to son to grandson, and so on, which depended upon each new generation to preserve and/or restore the works and the "names" of their predecessors. If the Assyrian kings each did their job as "Curator" or "Steward" of the family's heritage, they expressed the hope that they would not be forgotten--perhaps the closest they could get to achieving immortality.

Bhar, G. C. (2016). "In Search of Rationality in Human Longevity and Immortality." Mens Sana Monogr **14**(1): 187-213.

The human body is machine-like, but self-moving, self-regulating, and self-adjusting, governed by willpower and intelligence. Aging of the body is basically a maintenance problem and so it could perhaps be postponed by thorough and frequent maintenance. Aging brings on a cascade of ills and health problems leading to deterioration of physical, mental, emotional, and social dimensions of life. This paper deals with solution of the problem philosophically in the light of Indian scriptures without entering into traditional bioethical issues. With a meaningful reason for existence, life can be extended. Examining the scientific perspectives on aging, some common manipulations for its extension are discussed. These are calorie restriction, vitamin and antioxidant treatment, exercise and hormonal interventions, etc. Finally, the question of longevity is explored through pursuance of eternal value-based activity and spirituality in the tradition of Indian heritage.

Blagosklonny, M. V. (2006). "Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition." Cell Cycle **5**(18): 2087-2102.

While ruling out programmed aging, evolutionary theory predicts a quasi-program for aging, a continuation of the developmental program that is not turned off, is constantly on, becoming hyper-functional and damaging, causing diseases of aging. Could it be switched off pharmacologically? This would require identification of a molecular target involved in cell senescence, organism aging and diseases of aging. Notably, cell senescence is associated with activation of the TOR (target of rapamycin) nutrient- and mitogen-sensing pathway, which promotes cell growth, even though cell cycle is blocked. Is TOR involved in organism aging? In fact, in yeast (where the cell is the organism), caloric restriction, rapamycin and mutations that inhibit TOR all slow down aging. In animals from worms to mammals caloric restrictions, life-extending agents, and numerous mutations that increase longevity all converge on the TOR pathway. And, in humans, cell hypertrophy, hyper-function and hyperplasia, typically associated with activation of TOR, contribute to diseases of aging. Theoretical and clinical considerations suggest that rapamycin may be effective against atherosclerosis, hypertension and hyper-coagulation (thus, preventing myocardial infarction and stroke), osteoporosis, cancer, autoimmune diseases and arthritis, obesity, diabetes, macula-degeneration, Alzheimer's and Parkinson's diseases. Finally, I discuss that extended life span will reveal new causes for aging (e.g., ROS, 'wear and tear', Hayflick limit, stem cell exhaustion) that play a limited role now, when quasi-programmed senescence kills us first.

Chiu, C. P. and C. B. Harley (1997). "Replicative senescence and cell immortality: the role of telomeres and telomerase." Proc Soc Exp Biol Med **214**(2): 99-106.

Telomere shortening is correlated with cell senescence in vitro and cell aging in vivo. The telomere hypothesis suggests that telomere length serves as a mitotic clock for timing cellular replicative life span. Expression of telomerase stabilizes telomere length and allows for continual replication, or cell immortality. This article reviews recent evidences for the role of telomere length and telomerase in the regulation of cellular replicative life span. The therapeutic potential of manipulating telomerase expression and telomere length is also discussed.

Colarusso, C. A. (2011). "Death, rejuvenation and immortality in film: On Golden Pond (1981), Cat on a Hot Tin Roof (1958) and Cocoon (1985)." Am J Psychoanal **71**(2): 146-161.

This paper seeks to highlight the developmental tasks of late adulthood with the help of three Hollywood movies. These tasks include: (i) struggling to maintain physical integrity, (ii) handling the "wound of mortality", (iii) maintaining activity and sexuality, and (iv) becoming wise. Among other challenges faced by an individual during this phase of life are loss of love objects, illness and possible compromise of mental functions, de-cathexis of material possessions and coming to terms with one's approaching death. All sorts of healthy and unhealthy psychosocial maneuvers come to the surface as a result of these stresses. This paper illustrates these dilemmas and their potential solutions via a discussion of three movies.

Dalerba, P., et al. (2005). "Reconstitution of human telomerase reverse transcriptase expression rescues colorectal carcinoma cells from in vitro senescence: evidence against immortality as a constitutive trait of tumor cells." Cancer Res **65**(6): 2321-2329.

Although in vitro establishment of new colorectal carcinoma (CRC) cell lines is an infrequent event, we have observed that primary cultures of CRC can be repeatedly and reproducibly initiated following in vitro plating of tumor-derived epithelial cells. These cultures, however, usually display a short life span as they undergo a limited number of cell passages before entering a state of irreversible growth arrest. In this study, we show that short-lived CRC primary cultures lack constitutive telomerase activity and undergo a senescence process characterized by progressive telomere shortening. Moreover, transduction of these cells with a retroviral vector encoding human telomerase reverse transcriptase (hTERT) is sufficient to reconstitute telomerase activity and allow immortalization. Detailed molecular characterization of hTERT-immortalized CRC cell lines confirms their individual tumor origin by showing expression of colonic epithelial differentiation markers, such as cytokeratin-20 (CK20), full match with class I and class II human leukocyte antigen genotyping of autologous B-lymphoblastoid cells, and presence of somatic mutations in key cancer genes (KRAS2, APC) identical to those of the corresponding autologous original tumor tissues. Moreover, functional characterization of hTERT-immortalized CRC cell lines shows that they have a transformed phenotype, being able to form colonies in soft agar and tumors in severe combined immunodeficient mice. Most interestingly, immunohistochemical analysis of original tumor tissues indicates that short-lived CRC primary cultures, although hTERT-negative in vitro, derive from hTERT-positive tumors. Taken together, our data show that, in a least subset of CRC, biochemical pathways involved in maintenance of telomere length, such as telomerase, are not activated in a constitutive way in all tumor cells.

Drolet, J. L. (1990). "Transcending death during early adulthood: symbolic immortality, death anxiety, and purpose in life." J Clin Psychol **46**(2): 148-160.

Robert Jay Lifton has originated a comprehensive theory of development based on the human psychobiological need to symbolize death and life continuity. He calls this condition the sense of symbolic immortality and argues that life is threatened whenever death is not transcended. A Sense of Symbolic Immortality Scale was built and administered to two groups of young adults (N = 136) in order to test the hypothesis that symbolic immortality develops with age (Drolet, 1986). Templer's Death Anxiety Scale and Crumbaugh and Maholick's Purpose in Life Test also were administered. Results show that established adults have a sense of symbolic immortality and a purpose in life significantly stronger than those of young adults. They show a negative relation between death anxiety and purpose in life, while purpose in life correlates highly with the sense of symbolic immortality. Finally, the premise that the sense of symbolic immortality helps cope with the fear of death is supported.

Erenpreisa, J. and M. S. Cragg (2013). "Three steps to the immortality of cancer cells: senescence, polyploidy and self-renewal." Cancer Cell Int **13**(1): 92.

Metastatic cancer is rarely cured by current DNA damaging treatments, apparently due to the development of resistance. However, recent data indicates that tumour cells can elicit the opposing processes of senescence and stemness in response to these treatments, the biological significance and molecular regulation of which is currently poorly understood. Although cellular senescence is typically considered a terminal cell fate, it was recently shown to be reversible in a small population of polyploid cancer cells induced after DNA damage. Overcoming genotoxic insults is associated with reversible polyploidy, which itself is associated with the induction of a stemness phenotype, thereby providing a framework linking these separate phenomena. In keeping with this suggestion, senescence and autophagy are clearly intimately involved in the emergence of self-renewal potential in the surviving cells that result from de-polyploidisation. Moreover, subsequent analysis indicates that senescence may

paradoxically be actually required to rejuvenate cancer cells after genotoxic treatments. We propose that genotoxic resistance is thereby afforded through a programmed life-cycle-like process which intimately unites senescence, polyploidy and stemness.

Goldwert, M. (1985). "Otto Rank and man's urge to immortality." J Hist Behav Sci **21**(2): 169-177.

Otto Rank, one of Sigmund Freud's original followers, posited the existence of an "urge to immortality" as man's deepest drive. In his Psychology and the Soul, Rank traced the desire for immortality through four historical eras, with particular emphasis on the creativity of the hero and the artist. By the end of his life, Rank had not only repudiated orthodox psychoanalysis and developed then abandoned a psychology of the will, he had moved "beyond psychology" to a religious view of history and the nature of man.

Gordon, K., et al. (2014). "Immortality, but not oncogenic transformation, of primary human cells leads to epigenetic reprogramming of DNA methylation and gene expression." Nucleic Acids Res **42**(6): 3529-3541.

Tumourigenic transformation of normal cells into cancer typically involves several steps resulting in acquisition of unlimited growth potential, evasion of apoptosis and non-responsiveness to growth inhibitory signals. Both genetic and epigenetic changes can contribute to cancer development and progression. Given the vast genetic heterogeneity of human cancers and difficulty to monitor cancer-initiating events in vivo, the precise relationship between acquisition of genetic mutations and the temporal progression of epigenetic alterations in transformed cells is largely unclear. Here, we use an in vitro model system to investigate the contribution of cellular immortality and oncogenic transformation of primary human cells to epigenetic reprogramming of DNA methylation and gene expression. Our data demonstrate that extension of replicative life span of the cells is sufficient to induce accumulation of DNA methylation at gene promoters and large-scale changes in gene expression in a time-dependent manner. In contrast, continuous expression of cooperating oncogenes in immortalized cells, although essential for anchorage-independent growth and evasion of apoptosis, does not affect de novo DNA methylation at promoters and induces subtle expression changes. Taken together, these observations imply that cellular immortality promotes epigenetic adaptation to highly proliferative state, whereas transforming oncogenes confer additional properties to transformed human cells.

Haught, J. F. (2011). "Science, self, and immortality." Ann N Y Acad Sci **1234**: 70-75.

The following considers the concept of scientific naturalism in relation to life after death and contrasts three alternative perspectives on immortality of the soul, including naturalistic fatalism, otherworldly optimism, and long-suffering hope.

Hayflick, L. (1999). "[A brief overview of the discovery of cell mortality and immortality and of its influence on concepts about aging and cancer]." Pathol Biol (Paris) **47**(10): 1094-1104.

After having accomplished the miraculous performance that led us from conception to birth, then to sexual maturity and adulthood, natural selection failed to develop a more elementary mechanism capable of simply maintaining the results of this process forever. This failure is aging. Because few animals age in the wild, evolution could not give an advantage to animals with modifications due to aging. Natural selection benefits those animals that have the highest likelihood of effectively perpetuating their species because their vital systems have the larger reserve capacity they need to resist and survive predators, disease, injury, and extreme environmental conditions. Natural selection decreases after sexual maturity has been reached because at that stage the species would not derive additional advantages from individuals with larger physiological reserves. A species increases its likelihood of survival by investing its resources and energy into increasing its opportunities for fruitful reproduction rather than into prolonging its postreproductive life span. Most animals are mortal and undergo aging because investment of resources into keeping the body eternally youthful does not promote species survival as much as their investment into strategies that make reproduction more successful.

Heber-Katz, E., et al. (2006). "Conjecture: Can continuous regeneration lead to immortality? Studies in the MRL mouse." Rejuvenation Res **9**(1): 3-9.

A particular mouse strain, the MRL mouse, has been shown to have unique healing properties that show normal replacement of tissue without scarring. The serendipitous discovery that the MRL mouse has a profound capacity for regeneration in some ways rivaling the classic newt and axolotl species raises the possibility that humans, too, may have an innate regenerative ability. We propose this mouse as a model for continuous regeneration with possible life-extending properties. We will use the classical "immortal" organism, the hydra, for comparison and examine those key phenotypes that contribute to their immortality as they are expressed in the MRL mouse versus control mouse strains. The phenotypes to be

examined include the rate of proliferation and the rate of cell death, which leads to a continual turnover in cells without an increase in mass.

Johnson, T. E. (2005). "Genes, phenes, and dreams of immortality: the 2003 Kleemeier Award lecture." J Gerontol A Biol Sci Med Sci **60**(6): 680-687.

The 2002 Kleemeier Award from the Gerontological Society of America was awarded to Thomas E. Johnson, PhD, of the University of Colorado at Boulder. Dr. Johnson was the pioneer who first applied genetic analyses to the study of the aging processes in Caenorhabditis elegans and who introduced the nematode as an aging model. Longer life span was chosen as a surrogate marker for slowed aging. Here Dr. Johnson describes his role (s) in the isolation of age-1, the first longevity mutant, which can more than double the life span and which slows the rate of aging more than twofold. He also reviews research suggesting conservation of function and applicability to intervention by pharmacological targeting of the Age-1 pathway. Current work by biotechnology companies targets this and other basic discoveries in an attempt to postpone human aging.

Kartsev, V. M. (2014). "Phenoptosis in arthropods and immortality of social insects." Biochemistry (Mosc) **79**(10): 1032-1048.

In general, there are no drastic differences in phenoptosis patterns in plant and animal organisms. However, there are some specific features characteristic for insects and other arthropods: 1) their development includes metamorphosis with different biochemical laws at consecutive developmental stages; 2) arthropods can reduce or stop development and aging when in a state of diapause or temporal cold immobility; 3) their life cycle often correlates with seasonal changes of surroundings; 4) polymorphism is widespread - conspecifics differ by their lifespans and phenoptosis features; 5) lifespan-related sexual dimorphism is common; 6) significant situational plasticity of life cycle organization is an important feature; for example, the German wasp (Paravespula germanica) is obligatorily univoltine in the temperate zone, while in tropical regions its lifespan increases and leads to repeated reproduction; 7) life cycles of closely related species may differ significantly, for example, in contrast to German wasp, some tropical hornets (Vespa) have only one reproduction period. Surprisingly, many insect species have been shown to be subjected to gradual aging and phenoptosis, like the highest mammals. However, queens of social insects and some long-lived arachnids can apparently be considered non-aging organisms. In some species, lifespan is limited to one season, while others live much longer or shorter. Cases of one-time reproduction are rather rare. Aphagia is common in insects (over 10,000 species). Cannibalism is an important mortality factor in insects as well as in spiders. In social insects, which exist only in colonies (families), the lifetime of a colony can be virtually unlimited. However, in case of some species the developmental cycle and death of a colony after its completion are predetermined. Most likely, natural selection in insects does not lengthen individual lifespan, but favors increase in reproduction efficiency based on fast succession of generations leading to increased evolvability.

Krupp, G., et al. (2000). "Telomerase, immortality and cancer." Biotechnol Annu Rev **6**: 103-140.

Replication of eukaryotic linear chromosomes is incomplete and leaves terminal gaps. The evolutionary widely distributed solution to this "end replication" is twofold: chromosome ends are capped with telomeres, bearing multiple copies of redundant telomeric sequences, and the telomerase enzyme can add (lost) telomeric repeats. Telomerase in humans, as in all mammals, is ubiquitous in all embryonic tissues. In adults, telomerase remains active in germs cells, and, although down-regulated in most somatic tissues, telomerase is active in regenerative tissues and notably, in tumor cells. Telomerase activity is linked to cellular proliferation, and its activation seems to be a mandatory step in carcinogenesis. In contrast to mammals, indeterminately growing multicellular organisms, like fish and crustaceae, maintain unlimited growth potential or 'immortality' in all somatic tissues throughout their entire life. Also this cell immortalization is brought about by maintaining telomerase expression. Disease prognosis for human tumors includes evaluation of cell proliferation, based on the detection of proliferation markers with monoclonal antibodies. The significance of the classical marker Ki-67, and of a novel marker repp-86 are compared with semiquantitative telomerase assays. For tumor therapy, telomerase inhibitors are attractive tools. Results with telomerase knock-out mice have revealed promise, but also risk of this approach. On the other side, telomerase stimulation is attractive for expanding the potential of cellular proliferation in vitro, with possible applications for transplantation of in vitro expanded human cells, for immortalizing primary human cells as improved tissue models, and for the isolation of otherwise intractable products, like genuine human monoclonal antibodies.

Loeb, L. (1926). "Transplantation and Potential Immortality of Mammalian Tissues." J Gen Physiol **8**(5): 417-440.

1. Serial transplantation of tumors made it possible in 1901 and following years to draw the conclusion that various mammalian tissues have potential immortality. Serial transplantations of normal tissues did not succeed at first, because the homoioreaction on the part of the lymphocytes and connective tissue of the host injures the transplant. 2. In continuation of these experiments we found that cartilage of the rat can be transplanted serially to other rats at least for a period of 3 years. At the end of that time great parts of the transplanted cartilage and perichondrium are alive. 3. Not only the cartilage of young rats can be homoiotransplanted, but also the cartilage of very old rats which are nearing the end of life. By using such animals we have been able to obtain cartilage and perichondrium approaching an age of 6 years which is almost double the average age of a rat. 4. We found that cartilage can be homoiotransplanted more readily than other tissues for the following reasons: (a) While in principle the homoioreaction towards cartilage is the same as against other tissues, cartilage elicits this reaction with less intensity; (b) cartilage is better able to resist the invasion of lymphocytes and connective tissue than the majority of other tissues; (c) a gradual adaptation between transplant and host seems to take place in the case of cartilage transplantation, as a result of which the lymphocytic reaction on the part of the host tissue decreases progressively the longer the cartilage is kept in the strange host. 5. At time of examination we not only found living transplanted cartilage tissue, but also perichondrial tissue, which in response to a stimulus apparently originating in the necrotic central cartilage, had been proliferating and replacing it. These results suggest that it may perhaps be possible under favorable conditions to keep cartilage alive indefinitely through serial transplantations. 6. At the same time these experiments permit the analysis of the factors which are favorable or unfavorable to the continued life of the transplants. Favorable factors are: (a) Well preserved perichondrium around transplant; (b) cellular newly formed perichondrial cartilage- though it is doubtful whether such young cartilage cells allow a state of stable equilibrium. Host connective tissue does not invade transplant under these conditions. Unfavorable factors are: (a) Cartilage differentiation and the production of paraplastic substances (hyaline capsules in parts of transplant far removed from vessels and sources of oxygen and food; (b) cartilage necrosis when a still greater distance from nourishment exists; (c) disturbance of equilibrium between host connective tissue and transplant due to above conditions, resulting in (d) attack by host connective tissue on transplanted cartilage, which is the chief danger in the preservation of the life of the whole transplant 7. It is pointed out that also in old age there exist similar problems of disturbances of tissue equilibria, due to degenerative changes in certain parenchymatous structures and to proliferative processes on the part of connective tissue and glia elements together with increase in paraplastic structures.

McGregor, F., et al. (2002). "Molecular changes associated with oral dysplasia progression and acquisition of immortality: potential for its reversal by 5-azacytidine." Cancer Res **62**(16): 4757-4766.

This study has identified molecular changes characteristic of early oral cancer progression. We reported previously that acquisition of the immortal phenotype is an early event in oral cancer development (F. McGregor et al., Cancer Res., 57: 3886-3889, 1997); our current data indicate that about half of oral dysplasia cultures are immortal, and this is associated with loss of expression of retinoic acid receptor (RAR)-beta and the cell cycle inhibitor p16(ink4a) (p16), p53 mutations, and increased levels of telomerase/human telomerase reverse transcriptase mRNA. In contrast, increased expression of the epidermal growth factor receptor, known to be a characteristic of oral cancer, does not occur until after the dysplasia stage in squamous cell carcinomas. Acquisition of invasive properties as judged by an in vitro Matrigel invasion assay also does not occur until the carcinoma stage and is further increased in metastases. Interestingly, one atypical mortal dysplasia with a considerably extended life span has lost expression of RAR-beta and p16, but it still expresses only wild-type p53 (albeit at a higher level than normal) and has not activated telomerase. RAR-beta and/or p16 re-expression can be induced by treatment with 5-aza-2-deoxycytidine (Aza-C) in some immortal dysplasias, and this has been shown to be due to silencing of gene expression by promoter methylation. Aza-C treatment also down-regulated telomerase activity and human telomerase reverse transcriptase mRNA. Interestingly, with one dysplasia, Aza-C was able to reverse its immortal phenotype, as judged by morphological criteria and expression of the senescence-associated acid beta-galactosidase activity during terminal growth arrest; this immortal dysplasia was the only one in which Aza-C treatment not only down-regulated telomerase activity but also induced re-expression of both RAR-beta and p16. The possibility of reversing the immortal phenotype of some dysplasias by Aza-C may be of clinical usefulness.

Munne-Bosch, S. (2014). "Perennial roots to immortality." Plant Physiol **166**(2): 720-725.

Maximum lifespan greatly varies among species, and it is not strictly determined; it can change with

species evolution. Clonal growth is a major factor governing maximum lifespan. In the plant kingdom, the maximum lifespans described for clonal and nonclonal plants vary by an order of magnitude, with 43,600 and 5,062 years for Lomatia tasmanica and Pinus longaeva, respectively. Nonclonal perennial plants (those plants exclusively using sexual reproduction) also present a huge diversity in maximum lifespans (from a few to thousands of years) and even more interestingly, contrasting differences in aging patterns. Some plants show a clear physiological deterioration with aging, whereas others do not. Indeed, some plants can even improve their physiological performance as they age (a phenomenon called negative senescence). This diversity in aging patterns responds to species-specific life history traits and mechanisms evolved by each species to adapt to its habitat. Particularities of roots in perennial plants, such as meristem indeterminacy, modular growth, stress resistance, and patterns of senescence, are crucial in establishing perenniality and understanding adaptation of perennial plants to their habitats. Here, the key role of roots for perennial plant longevity will be discussed, taking into account current knowledge and highlighting additional aspects that still require investigation.

Murphy, N. (2011). "Immortality versus resurrection in the Christian tradition." Ann N Y Acad Sci **1234**: 76-82.

For those in contemporary society who believe in an afterlife, there are a number of views available. The most common may be based on belief in an immortal soul. However, the early Christian account was, instead, bodily resurrection. As Christianity moved throughout the Mediterranean world, apologists and theologians adapted their teaching on human nature and the afterlife to Greek and Roman philosophies. By the time of Augustine (d. 430), the doctrines of body-soul dualism and immortality of the soul were firmly entrenched in Christian teaching. The incorporation of the concept of an immortal soul into Christian accounts of life after death produced a hybrid account. The body dies, the soul (at least of those who were to be saved) travels to heaven. At the end of history, there would be a general resurrection, and the souls would be reunited with their bodies, although the bodies would be in a transformed, indestructible state. This hybrid account of life after death went largely uncontested until the twentieth century. In this essay, I describe this history and argue for a return to the early Christian view of humans as a unity, not a duality, and for belief in resurrection of the body as the appropriate expectation for eternal life. This would not only be truer to Christian sources, but, valuable, I believe, in focusing Christian attention on the need to care for the environment.

Olshansky, S. J. and B. A. Carnes (2013). "Zeno's Paradox of Immortality." Gerontology **59**(1): 85-92.

Scientists who speculate on the future of human longevity have a broad range of views ranging from the promise of immortality, to radical life extension, to declines in life expectancy. Among those who contend that radical life extension is already here, or on the horizon, or immortality is forthcoming, elements of their reasoning appear surprisingly close, if not identical, to a famous mathematical paradox posed by the ancient Greek mathematician known as Zeno. Here we examine the underlying assumptions behind the views that much longer life expectancies are forthcoming or have already arrived, and place their line of reasoning within the context of a new Zeno paradox described here as The Paradox of Immortality.

Petralia, R. S., et al. (2014). "Aging and longevity in the simplest animals and the quest for immortality." Ageing Res Rev **16**: 66-82.

Here we review the examples of great longevity and potential immortality in the earliest animal types and contrast and compare these to humans and other higher animals. We start by discussing aging in single-celled organisms such as yeast and ciliates, and the idea of the immortal cell clone. Then we describe how these cell clones could become organized into colonies of different cell types that lead to multicellular animal life. We survey aging and longevity in all of the basal metazoan groups including ctenophores (comb jellies), sponges, placozoans, cnidarians (hydras, jellyfish, corals and sea anemones) and myxozoans. Then we move to the simplest bilaterian animals (with a head, three body cell layers, and bilateral symmetry), the two phyla of flatworms. A key determinant of longevity and immortality in most of these simple animals is the large numbers of pluripotent stem cells that underlie the remarkable abilities of these animals to regenerate and rejuvenate themselves. Finally, we discuss briefly the evolution of the higher bilaterians and how longevity was reduced and immortality lost due to attainment of greater body complexity and cell cycle strategies that protect these complex organisms from developing tumors. We also briefly consider how the evolution of multiple aging-related mechanisms/pathways hinders our ability to understand and modify the aging process in higher organisms.

Petricciani, J. C., et al. (1987). "Early passage primate cell immortality is independent of

tumorigenicity." In Vitro Cell Dev Biol **23**(7): 523-526.

Seven continuous primate cell lines were tested in three systems (nude mice, muscle organ culture, and soft agarose) for their ability to express characteristics usually associated with malignant cell lines. Five of the seven cell lines failed to produce tumors in nude mice, failed to show a tumor-like pattern of growth in muscle organ culture, and failed to produce colonies in soft agarose. The remaining two cell lines showed different degrees of tumorigenicity in nude mice, and gave frankly positive results in the two in vitro assays. In addition, one of these lines appeared to progress from potential to overt tumorigenicity. We conclude that acquisition of infinite life in primate cell lines is not invariably equivalent to the ability to form tumors.

Rahman, R., et al. (2009). "Cellular immortality in brain tumours: an integration of the cancer stem cell paradigm." Biochim Biophys Acta **1792**(4): 280-288.

Brain tumours are a diverse group of neoplasms that continue to present a formidable challenge in our attempt to achieve curable intervention. Our conceptual framework of human brain cancer has been redrawn in the current decade. There is a gathering acceptance that brain tumour formation is a phenotypic outcome of dysregulated neurogenesis, with tumours viewed as abnormally differentiated neural tissue. In relation, there is accumulating evidence that brain tumours, similar to leukaemia and many solid tumours, are organized as a developmental hierarchy which is maintained by a small fraction of cells endowed with many shared properties of tissue stem cells. Proof that neurogenesis persists throughout adult life, compliments this concept. Although the cancer cell of origin is unclear, the proliferative zones that harbour stem cells in the embryonic, post-natal and adult brain are attractive candidates within which tumour-initiation may ensue. Dysregulated, unlimited proliferation and an ability to bypass senescence are acquired capabilities of cancerous cells. These abilities in part require the establishment of a telomere maintenance mechanism for counteracting the shortening of chromosomal termini. A strategy based upon the synthesis of telomeric repeat sequences by the ribonucleoprotein telomerase, is prevalent in approximately 90% of human tumours studied, including the majority of brain tumours. This review will provide a developmental perspective with respect to normal (neurogenesis) and aberrant (tumourigenesis) cellular turnover, differentiation and function. Within this context our current knowledge of brain tumour telomere/telomerase biology will be discussed with respect to both its developmental and therapeutic relevance to the hierarchical model of brain tumourigenesis presented by the cancer stem cell paradigm.

Rauser, C. L., et al. (2003). "Aging, fertility, and immortality." Exp Gerontol **38**(1-2): 27-33.

Evolutionary theory suggests that fecundity rates will plateau late in life in the same fashion as mortality rates. We demonstrate that late-life plateaus arise for fecundity in Drosophila melanogaster. The result qualitatively fits the evolutionary theory of late life based on the force of natural selection. But there are a number of alternative interpretations. Fecundity plateaus could be secondary consequences of mortality-rate plateaus. Female fecundity plateaus might arise from diminished male sexual function. Another alternative hypothesis is analogous to male sexual inadequacy: nutritional shortfalls. These may arise later in life because of a decline in female feeding or digestion. If some females have a life-long tendency to lay eggs at a faster rate, but die earlier, then aging for fecundity could arise from the progressive loss of the fast-layers, with the late-life plateau simply the laying patterns of individual females who were slow-layers throughout adult life. If this type of model is generally applicable to late life, then we should find that the females who survive to lay at a slow but steady rate in late life have a similar laying pattern in mid-life.

Rose, M. R. and L. D. Mueller (2000). "Ageing and immortality." Philos Trans R Soc Lond B Biol Sci **355**(1403): 1657-1662.

The concept of the force of natural selection was developed to explain the evolution of ageing. After ageing, however, comes a period in which mortality rates plateau and some individual organisms could, in theory, live forever. This late-life immortality has no presently agreed upon explanation. Two main theories have been offered. The first is heterogeneity within ageing cohorts, such that only extremely robust individuals survive ageing. This theory can be tested by comparisons of more and less robust cohorts. It can also be tested by fitting survival data to its models. The second theory is that late-life plateaus in mortality reflect the inevitable late-life plateau in the force of natural selection. This theory can be tested by changing the force of natural selection in evolving laboratory populations, particularly the age at which the force plateaus. This area of research has great potential for elucidating the overall structure of life-history evolution, particularly the interrelationship between the three life-history phases of development, ageing and immortality.

Ryan, P. A., et al. (1994). "Failure of infinite life span human cells from different immortality

complementation groups to yield finite life span hybrids." J Cell Physiol **159**(1): 151-160.

The observation that fusion of infinite life span cells with finite life span cells produces hybrid cells with finite life spans led to the conclusion that an infinite life span in culture is a recessive trait resulting from loss of the function of a gene or genes that contribute to an active program for cellular senescence. Furthermore, finding that certain pairs of infinite life span cells, when fused to one another, can complement each other to yield finite life span hybrids allowed 30 infinite life span cell lines to be assigned to four immortality complementation groups (Pereira-Smith and Smith, 1988, Proc. Natl. Acad. Sci. U.S.A., 85:6042). In the present study, we fused a chromosomally stable, near diploid, morphologically normal, infinite life span cell strain, designated MSU-1.1, with its normal, finite life span, precursor cell strain and obtained finite life span hybrids, as expected if infinite life span in culture is a recessive trait. However, 14 of the 14 hybrids from our fusions of MSU-1.1 cells with representative cell lines from each of the four immortality complementation groups, and 38 of the 39 hybrids from our fusions of infinite life span cells that have been reported to complement each other, failed to exhibit finite life spans. This result suggests that infinite life span cells cannot complement each other to yield finite life span hybrids. In examining this unexpected result, we obtained evidence that long-term dual drug selection can be deleterious to hybrid cells even though they carry resistance markers for both drugs, indicating that the cell death of such hybrids observed in other studies may have resulted from the cytotoxic effect of long-term drug selection, rather than from senescence.

Schafer, D. (2017). "["Life is short". Rejuvenation and immortality from a historical perspective]." Dtsch Med Wochenschr **142**(25): 1901-1906.

To be young and immortal: That is the dream of humanity. Medical and civilizing progress have led to a life expectancy unthinkable a few centuries ago. Physicians wonder where it will all end. And after all, does it make sense to live forever? A look back in history and literature can help to relativize (post) modern utopias.

Seidel, A. (2005). "Facing immortality." Int J Appl Philos **19**(1): 85-104.

This study is primarily a call to philosophers to attend the concerns raised by the increasing possibility of indefinitely extended human life. While these concerns are largely moral and socio-political, questions arising from this possibility are seen to involve other philosophical areas, including epistemology. Starting with the age-old desire for extended, enjoyable life, possible strategies for realizing such life are considered. Such realization is shown to conflict with the desire for children. Various reasons for choice between the alternatives of indefinitely extended life and what is currently understood to be a normal life, including the possibility of offspring, are examined. Competing social visions are sketched for the purpose of resolving this dilemma. It is argued that humanity's likely choice from among the competing social sketches favors the decision for extended life against that for limited lifespan with the possibility of children. Assuming that the extended life will be a life of learning leads to epistemological considerations regarding what is to be learned.

Shukla, S., et al. (2010). "Telomere--the twilight to immortality." J Assoc Physicians India **58**: 553-560.

Besides forming a very important component of the chromosome, the telomeres have extremely significant modes of action and functions, right from maintaining a basic infrastructure and integrity of the chromosome vis a vis the other chromosomes, telomeres are responsible for the cell divisions and replicative senescence of the cell. The number of mitotic divisions which a cell will go through in its life span while passing through the cell cycle is governed inturn by these telomeres, the crux of the entire functioning of these chromosomal components suggests that they are the ticking clocks of the cell and when they diminish or are worn out so does the cell reach it's senility at the fag end of it's replicative life--resulting fate being--the cell is sent to it's grave yard (the final destination). Clinical implications include--regulation of cell life spans, regulating the cell's replicative behavior and it's utility in forming cells which usually are impossible to divide or replicate, telomeres regulate the cloning process,the telomeres play a major role in predicting the fate of a neoplastic cell and finally enhancing the life span of a single cell, the organ, the body as a whole by enzymes which expand the telomeres--the telomerase.

Trent, B. (2004). "The future of immortality." Humanist **64**(3): 11-15.

Trent shares his perspectives on the mechanics of future immortality and death, which are being laid bare in laboratories around the world. He reiterates that even among new immortals, there will likely be people who, after a full life of two hundred or two million years, will decide that enough is simply enough, and that death may be as optional as the hair dye.

Walen, K. H. and M. R. Stampfer (1989). "Chromosome analyses of human mammary epithelial

cells at stages of chemical-induced transformation progression to immortality." Cancer Genet Cytogenet **37**(2): 249-261.

Benzo (a)pyrene induced extended life (EL) (i.e., a longer than normal proliferative lifespan before senescence) of human breast cells in culture. From many EL cell cultures immortalized cells emerged only once in each of two separate experiments. The original EL cells were mostly normal diploid with only a small percentage of tetraploid cells. The two immortalized cell lines, however, were near diploid, each containing a set of chromosomal aberrations that were present in all the cells analyzed, confirming the clonal origin of both cell lines. For cell line 184A1 the aberrations consisted of deficiencies only, whereas a combination of deficiencies and duplications characterized the 184B5 line. None of the individual aberrations of each set were shared by both cell lines. Both sets of aberrations have remained stable for over 150 population doublings, while some of the other chromosomes showed breakage and reunions. These data are discussed in regard to types of mutations in the sequence of changes from primary to immortalized cells, and it is concluded that the sets of aberrations most likely originated as multiple events in a single cell.

Watanabe, H., et al. (2009). "Immortality and the base of multicellular life: Lessons from cnidarian stem cells." Semin Cell Dev Biol **20**(9): 1114-1125.

Cnidarians are phylogenetically basal members of the animal kingdom (>600 million years old). Together with plants they share some remarkable features that cannot be found in higher animals. Cnidarians and plants exhibit an almost unlimited regeneration capacity and immortality. Immortality can be ascribed to the asexual mode of reproduction that requires cells with an unlimited self-renewal capacity. We propose that the basic properties of animal stem cells are tightly linked to this archaic mode of reproduction. The cnidarian stem cells can give rise to a number of differentiated cell types including neuronal and germ cells. The genomes of Hydra and Nematostella, representatives of two major cnidarian classes indicate a surprising complexity of both genomes, which is in the range of vertebrates. Recent work indicates that highly conserved signalling pathways control Hydra stem cell differentiation. Furthermore, the availability of genomic resources and novel technologies provide approaches to analyse these cells in vivo. Studies of stem cells in cnidarians will therefore open important insights into the basic mechanisms of stem cell biology. Their critical phylogenetic position at the base of the metazoan branch in the tree of life makes them an important link in unravelling the common mechanisms of stem cell biology between animals and plants.

Wisman, A. and N. A. Heflick (2016). "Hopelessly mortal: The role of mortality salience, immortality and trait self-esteem in personal hope." Cogn Emot **30**(5): 868-889.

Do people lose hope when thinking about death? Based on Terror Management Theory, we predicted that thoughts of death (i.e., mortality salience) would reduce personal hope for people low, but not high, in self-esteem, and that this reduction in hope would be ameliorated by promises of immortality. In Studies 1 and 2, mortality salience reduced personal hope for people low in self-esteem, but not for people high in self-esteem. In Study 3, mortality salience reduced hope for people low in self-esteem when they read an argument that there is no afterlife, but not when they read "evidence" supporting life after death. In Study 4, this effect was replicated with an essay affirming scientific medical advances that promise immortality. Together, these findings uniquely demonstrate that thoughts of mortality interact with trait self-esteem to cause changes in personal hope, and that literal immortality beliefs can aid psychological adjustment when thinking about death. Implications for understanding personal hope, trait self-esteem, afterlife beliefs and terror management are discussed.

Wynford-Thomas, D., et al. (1989). "Suppression of transformation and immortality in human/Chinese hamster fibroblast hybrids--a model for suppressor gene isolation." Int J Cancer **43**(2): 293-299.

Somatic cell hybrids were produced by fusion of normal human (foreskin) fibroblasts and a transformed Chinese hamster fibroblast line V79-8. Overall, approximately 30% of hybrid clones showed stable reversion to normal morphology and growth control in vitro as shown by serum and anchorage dependence. In one-third of these clones, senescence was observed after a number of generations similar to that required for the human fibroblast parent cells to senesce. The remainder appear to be immortal. Normal human chromosomes can therefore restore growth control with or without finite life-span to this transformed cell. V79 cells were found to be transfectable at an efficiency compatible with detection of single-copy gene transfer from genomic DNA. Furthermore, these cells were exceptionally sensitive to negative ("suicide") selection. Taken together, our data suggest that the V79 line represents an ideal system for isolation of human tumour suppressor genes.

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