Review of: "On the Origin of Aging by Means of Natural Selection"

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Reviewer Comments

Richard Walker has a Big Idea[1]. Walker's hypothesis is that aging in humans and other mammals has a single cause—the loss of "regulatory redundancy." According to Walker, a developmental program, regulatory redundancy, supports cell health of young adults during their reproductive years. After 30 years of age, the programmed regulatory redundancy process begins to decay, resulting in aging and death. So as not to misrepresent Walker's Big Idea, I quote from his abstract:

"The present theory describes the single cause of human aging consistent with Darwin's evolutionary requirement for selection of adaptive traits. It describes an emergent property of the developmental program that is expressed upon completion of ontogenesis. It involves redundant expression of regulatory processes from the last stage of the developmental program. That mechanism subsequently preserves a non-aging, stable interval of unchanging natural selection during which reproductive fitness is achieved. Thereafter, loss of developmental program regulatory redundancy due to reliability limits, stochastic mutation accumulation, reproductive and a specific type of DNA damage, initiates aging which causes an inexorable decline in strength of natural selection to begin."

Here, I provide a pragmatic description of Walker's Big Idea by placing his hypothesis inside the context of the chronological stages of programmed development in humans from fertilized egg to reproductive adult. I summarize the types of cell death, the triggers of cell death that lead to aging in humans. I summarize several theories of aging by natural selection, including Walker's theory. Lastly, I offer insight into why we age and die.

Walker's Big Idea

Walker's Big Idea is a hypothetical model of programmed development from conception through development to sexual maturity, aging and death. Walker classifies his model of programmed development in three categories: morphogenesis, morphostasis, and morpholysis (Fig. 1). During *morphogenesis*, the rate of cell reproduction (the division of one cell into two daughter cells) exceeds the rate of cell death, resulting in the growth and development of a human from a single fertilized egg to an adult composed of 20-30 trillion cells. During *morphostasis*, the rate of cell reproduction is equal to the rate of cell death, resulting in healthy sexually mature adults during their prime reproductive years. During *morpholysis*, the rate of cell death exceeds the rate of cell reproduction, resulting in aging, organ failure, and death. In the following sections, I elaborate on the complex stages of human development from conception to aging and death beginning with a

focus on cell reproduction, growth, specialization, dysfunction, and death.

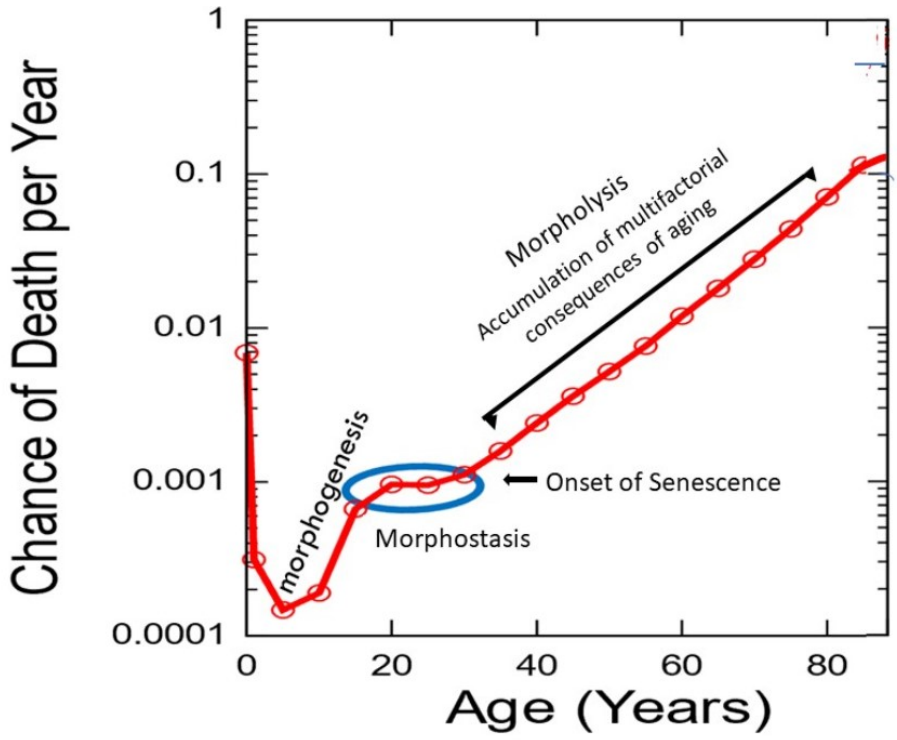

Figure 1. Walker's plot of the Gompertz–Makeham "law of mortality." In humans, morphostasis (circled) lasts for approximately a decade between growth during morphogenesis and the onset of exponentially increasing morpholysis. This figure is in the public domain and was reproduced and modified without permission from Volume 54, Number 14 United States Life Tables, 2003 by Elizabeth Arias, Ph.D., Division of Vital Statistics.

Cells as the basis unit of life

Cells are the basic unit of all life on our planet. Whether cells exist as solitary organisms or as a cooperative family of specialized cells in the body of a multicellular human, each microscopic cell is a living, breathing, behaving organism that grows and then reproduces two identical daughter cells, twins that are 50% the size of the female parental cell, *i.e.,* mitosis. Cells are composed of three features: a lipid membrane that controls what goes in and out of the cell; cytoplasm that fills the cell, supporting and nourishing the cell's internal organs (microscopic organelles); and the nucleus, the organelle that contains most of the genetic information in the form of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) divided among multiple chromosomes. The "genome" is the sum total of the DNA sequences divided among multiple chromosomes within each cell of an individual's body. Within the body, the genome of each cell is identical. However, like a keyboard with 88 keys that can produce an infinite number of melodies, it is the differential expression of our 46,000 genes that produces cells with specialized functions.

In humans during sexual reproduction, *i.e.,* meiosis, parent cells with 46 chromosomes undergo two cycles of cell division

but only one round of DNA replication. During the first cell division, each daughter cell as the same number of chromosomes as the female parent cell, 46. During the second division, the 46 chromosomes are randomly assorted into two gamete cells with 23 chromosomes each. In humans, randomly assorted chromosomes during the second cell division produces 8 million gametes with unique genomes. In humans, sperm have been stripped of all organelles except the nucleus, augmented with a neck and tail for motility, and a few energy organelles (mitochondria) to power the swim through a female's reproductive organs to reach the egg. Without the full complement of organelles and cytoplasm to initiate cell reproduction, sperm are incapable of producing new life. In contrast, eggs are obese cells overstocked with proteins and lipids for supporting the initial stages of embryonic development. Once an egg has received the sperm's genome—a second set of chromosomes—cell reproduction begins. The egg is totipotent, with the capacity to reproduce generations of daughters capable of morphing into 200 specialized cells forming the organs and organ systems within a multicellular body. In short, a female's egg produces the next generation of offspring; a male's sperm diversifies a female's offspring.

Morphogenesis

All life begins and ends with cells. In multicellular humans, life begins as a fertilized egg protected and provisioned by the female's body. We grow and develop into a multicellular embryo by cell reproduction and cell specialization in trillions of highly choreographed social interactions and migrations until each cell finds its final destination.

In the first hours after fertilization, the totipotent egg divides into identical totipotent cells. After four cell division cycles, the 16 totipotent cells begin to differentiate into three tissue layers—the outer ectoderm, the inner endoderm, and the middle mesoderm. The solid ball of differentiating cells forms a hollow ball, the blastocyst. Once imbedded into the mother's body, nutrients fuel rapid cell reproduction and cell differentiation resulting in the formation of an embryo. Most organs are formed within three months of embryo development, but not all are functional. The brain and spinal cord continue to develop throughout the gestation period. Birth signifies the end the embryo stage of development and the beginning of the infant stage of development. Walker rightly calls this pre-birth process "programmed development." If the developmental program fails at any point in the sequential process, the embryo fails.

During the first year after birth, infants grow in size and shape, while gaining skills such as babbling, smiling, sitting, crawling, teething, standing, and walking. Compared to the newborn, the average one-year old infant is twice as long and three times as heavy. Again, if the developmental program fails, the infant fails.

Growth and development from toddler to six years is less rapid relative to the embryo and infant stages of development. In humans, toddler milestones include toilet training, running, climbing, and language. By age six, permanent teeth appear, speech is fluent, and non-kin friendships are developing.

Gamete production signals puberty, the process of physical changes in which a juvenile matures into an adult capable of sexual reproduction. Hormonal signals from the brain initiate growth and development of the gonads—egg-producing ovaries in the female and sperm-producing testicles in a male.

Adolescence is a transitional period between puberty and adulthood. For humans and most mammals, the morphogenesis

stage of growth and development ends, not when individuals reach puberty, but when individuals have reached their final adult height. Although skeletal height stops at adulthood, body mass varies depending on muscle mass, storage proteins, and fat storage cells.

Morphostasis

In humans from 18 to 30 years, cellular processes reach an optimal level of functional physiological homeostasis in which the internal environment is stable despite changes in the external environment. For example, body temperature, fluid balance, pH, blood sugar level, sodium, potassium and calcium ions remain stable within pre-set limits referred to as the homeostatic range. During morphostasis, rates of cell reproduction and differentiation are equivalent to rates of cell death.

Morpholysis

In humans, the aging process begins in earnest around 28 to 30 years. Aging occurs when the rate of cell injury and death exceeds the rate of cell reproduction. As cells die without replacement, our appearance undergoes subtle changes. Wrinkles, moles, spots, sagging, and a general thinning of skin occur. Hair, bone and muscle mass decline. Eyes, hearing, and memory decline. The chances of experiencing cancers, arthritis, Type 2 diabetes, cardiovascular disorders, gut disorders, and metabolic disorders increases.

Body cells, *i.e.,* soma cell, die in five ways: necrosis (cell injury), phagocytosis (cell cannibalism), autophagy (self-cannibalism), apoptosis (cell suicide), and senescence (cell menopause). Necrosis is the premature death of cells caused by traumas external to the cell or cell tissue such as diet, bacterial infections, poisons, venoms, injuries, over-exposure to sun, heat or cold, fire, smoke, floods, and pollutants. Injured cells lose membrane integrity causing an uncontrolled release of cytoplasm and proteins into the extracellular matrix[2]. If untreated, decomposing cells and cell debris at or near the injured site build up. Without surgical debridement to remove uncontrolled necrosis, gangrene sets in. The top three leading causes of death in the United States are heart disease, cancer, and COVID-19. Heart disease was the leading cause of death worldwide[published by Statista Research Department, Oct 6, 2023].

Phagocytosis is a vital defense mechanism within immune systems of multicellular organisms such as humans and other mammals. Phagocytes are motile cells that ingest harmful bacteria, foreign particles and dead or dying cell. Phagocytosis occurs when phagocytes detect and ingest injured or infected cells (cell cannibalism) or bacteria (cell predation). The ingested material is dissolved in the phagosome (stomach) of the phagocyte.

Autophagy is a programmed degradation process (self-cannibalism) during times of resource scarcity or stress. During autophagy, a cell recycles some of its internal macromolecules—proteins and organelles—that are damaged or worn out. Cells have the ability to recover when resources are once again abundant. However, if the stress is chronic, cells die and are ingested by phagocytes. Cell autophagy is linked to aging, neuropathy, and malignant tumors.

Cell apoptosis is a programmed and highly choreographed process of cell suicide[3,4]. Apoptosis and autophagy are triggered by the same stimulating factors, but the threshold for initiating each process differs[5]. During embryo development, apoptosis provides the space that allows for the separation of organs as they develop and function

independently from thick layers of shared tissue. As an example, apoptosis eliminates webbing during the formation of fingers and toes. Children and adolescents lose 20-30 billions cells a day by apoptosis; adults lose 50 to 70 billion cells each day. For an adult human or other mammal to maintain healthy morphostasis, each organ system must maintain an balance between the death of old, worn out cells and the birth of new healthy cells. As adults, when rates of cell reproduction grossly exceed rates of cell apoptosis, excess cells become tumors, benign and cancerous. On the other hand, higher rates of cell suicide relative to cell reproduction leads to neurodegenerative diseases including Huntington's disease, Alzheimer's disease, or Lou Gehrig's disease. In summary, cell apoptosis is an evolutionarily conserved process that is responsible for the programmed culling of cells during morphogenesis and the maintenance of morphostasis within and across adult organ systems. The apoptosis process (pathway) is controlled by the BCL-2 family of proteins, which contains both pro-survival and pro-apoptotic proteins that balance the decision between cell life and cell death[6].

Cell senescence (cell menopause) is the irreversible cessation of cell reproduction. The causes of cell senescence include acute and chronic stress, DNA damage, telomere shortening, oxidative stress, oncogenes, cell fusion, and other factors[7]. The accumulation of menopausal cells in a state of suspended animation contributes to aging, cancer, and neurodegeneration.

Although cell senescence and aging are correlated, we do not know if senescence causes aging or is an effect of other processes such as Walker's regulatory redundancy degradation. In the following section, I describe a few of the causes of aging.

How we age

Causes of aging fall into two categories: genes or stochastic damage[8]. In humans, 75% of variation in our lifespan has extrinsic causes including famine, flood, fire, disease, war, occupation, accidents, injuries, diet, or other lifestyle habits; 25% is inherited [9]. Intrinsic causes of cell death include telomere shortening, stem cell dysfunction, epigenetics (environmentally triggered changes in gene expression), and DNA repair dysfunction.

Telomeres are strands of repetitive DNA at the ends of linear chromosomes that protect chromosomes from degradation. Each time a parental cell reproduces, the telomeres of the chromosomes within the nucleus of her daughter cells shorten. Once the telomere is lost, cells can no longer reproduce. Aging and death follows. In gametes, an enzyme—telomerase—extends the length of the telomere to prevent chromosomal degradation. However, the overproduction of telomerase in soma cells leads to cancer. The dilemma is how to activate telomerase to the level of extending critically short telomere in "old cells" without inducing abnormal growth [10].

Stem cells are totipotent. As stem cells age, their ability to differentiate into the various cell types deteriorates, resulting in various aging-associated disorders in humans[11,12]. In mice, the homeobox gene "*caudal* is a candidate for managing age-related stem cell dysfunction[13].

Epigenetics is the study of how the environment changes the behavior of genes without changes their DNA sequences. As humans age, environmental stressors trigger predictable epigenetic changes[14] by producing enzymes that suppress

the genes that build the proteins that repair damaged DNA [15]. DNA repair of damaged or aging cells is vital to maintaining healthy growth and reproduction.

Most scientists view aging as a complex multifactorial process. Without DNA repair, cells accumulate large amounts of DNA damage, stop reproducing and die by apoptosis [8], resulting in accelerated physiological and cognitive aging in mammals[9]. To date, no single cause fully explains the causes of DNA damage in aging humans or other multicellular organisms[10]. Moreover, no known intervention permanently stops or reverses the aging process. If, in the future, we are able to definitely link the ultimate cause of cell aging to DNA double-strand breaks[9], then Walker's idea of a single cause of aging, degradation of a regulatory redundancy, might have validity. The question of why we age remains poorly understood. In the following section, I reflect on theories of aging by natural selection.

Theories on why we age

Theories on why we age and die depends on who benefits, *i.e., cui bono*?[16]. In humans, the evolution of aging by natural selection *per se* is antithetical, as it seems to lack benefit at the level of the aging individual.

In the mid-1800s, August Weismann, a respected biologist and colleague of Darwin, proposed that aging and death evolved by natural selection to benefit the species, not the individual[10]. Weismann speculated that eliminating older injured members of a species paved the way for the next generation of young healthy members. Most scientists today disregard a species-level explanation for why we age.

In the mid-1900s, Peter Medawar proposed the mutation accumulation theory of aging[17]. Medawar speculated that sometime in our ancestry, gene mutations that caused aging arose. However, according to Medawar's model, aging genes are suppressed during the first two stages of development—morphogenesis and morphostasis—and expressed only during the last stage of development—morpholysis. Because aging genes expressed themselves only late in life, after the reproductive years, parental fitness was not impacted by natural selection processes such as starvation or predation. Hence, Medawar's late-in-life aging genes entered our gene pool by genetic drift. Medawar reasoned that late-in-life aging gene remain in our gene pool because people reproduce despite its presence in our genome.

In his paper, *On the origin of aging by means of natural selection*, Walker justifiably dismisses tradeoff models of aging as none describes the benefit of aging, *de novo* by natural selection, relative to a non-aging state. Both Medawar and Walker connect their models to the three stages of development—morphogenesis, morphostasis, and morpholysis—but the mechanisms of their models differ. Whereas Medawar's aging genes are suppressed during morphogenesis and morphostasis, Walker's regulatory redundancy program is expressed during these two stages of development and reproduction. Likewise, whereas Medawar's aging genes are expressed during the last morpholysis stage of development, Walker's regulatory redundancy program degrades, resulting in aging and death. Neither model represents a *de novo* mechanism of aging; neither model compares the parental fitness benefits with or without the aging processes.

Who benefits from aging?

We cannot address this question from a human, parental fitness perspective, but we can address it from the perspective of

the first molecule to replicate herself, RNA Eve. At the level of replicating molecules, death and destruction are unavoidable—always have been, always will be. Let us circle back in time to when replicating molecules came into being.

Earth's journey as a hot rock covered by a toxic orange haze, into a cool rock with blue oceans teaming with fish and green continents occupied with herds of migrating mammals, is a consequence of uncountable, unspeakably violent events—beginning with its formation circa 4.5 billion years ago from an exploding supernova. Early after its formation into a planet with a thin crust, layers of molten elements, and a highly radioactive solid core, Earth was struck a glancing blow by small hot-rock planet that generated a rotational spin fast enough to produce currents of electricity that, in turn, formed a protective magnetic field. These currents, composed of molten iron and nickel, are hundreds of miles wide and flow at thousands of miles per hour as the earth rotates. Earth's powerful magnetic field provides a shield that protects the future, exceedingly delicate replicating molecules from destruction by deadly UV radiation. From the beginning of our planetary system, solar radiation has been the sole purveyor of life and death.

For the first billion years after Earth's formation, countless bombardments of icy comets established cool shallow seas. Asteroids delivered metallic and mineral elements. Amino acid molecules arrived as well[18]. During earth's second billion years, RNA Eve emerged as the first complex molecule to replicate itself[19]. processes. How did RNA Eve survive and thrive death by violent events and decay by unavoidable copy errors? While most of RNA Eve's daughters did not survive, a few did.

Copy errors produce new RNA variants—those that were unable to replicate themselves decayed into carbons, hydrogen, oxygen, nitrogen and phosphate atoms. Innovative RNA variants produced proteins with specialized functions that benefitted themselves and neighboring RNA variants. Together, RNA variants found a way to build a membrane-bound biosphere, the first protocell. Once enclosed inside a protective membrane, RNA variants and other molecules evolved in earnest as carriers of genetic instructions for building large proteins, structural and enzymatic. DNA Eve appeared on the scene later and proved to be more stable than RNA as a permanent repository of genetic information. DNA Eve built simple cells, prokaryotes, which eventually led to the dynasty of cyanobacteria. During its third and into its fourth billion years of age, Earth developed into an older, calmer, stable, less violent planet. Niches of opportunity expanded. The progeny of DNA Eve produced the first complex cell, the eukaryotes, that gave rise to the dynasties of coral, sharks, dinosaurs, and mammals. Life flourished because the diverse progeny of DNA Eve built complex societies of cells that could swim, walk or fly using sensory systems that converted energy into taste, smell, hearing, touch, sight, and electromagnetism with the goal of including eyes, ears, tongues, noses, skin, built vessels. To build complex multicellular humans from one fertilized egg requires the overproduction of daughter progeny and the culling of daughter progeny by apoptosis when negative space is required for organs, appendages and digits.

Let us now circle back to the evolution of aging in humans. We are social mammals without claws, canines, or armor to protect us from predators. We are an easy meal on two legs. Like schooling fish when sharks attack, our best defense is safety in numbers. Children and aging non-reproducing adults provide a buffer against predators. The elderly are repositories of information needed by their offspring to survive and reproduce. Prior to our agricultural revolution, aging family members retained and shared spatial and temporal maps and calendar memories for when and where to locate

medicinal plants, food, water, and shelters. Relative to dying after reproduction, the presence of aging elders was an innovation that ensured the survival of DNA Eve's progeny.

Can we achieve immortality?

According to a number of scientists, aging and death may no longer be inevitable[20]. Reprogramming and cloning human cells to regenerate organs and tissues might put the body into a state of constant renewal, or as Harris suggests, maybe we can switch off the genes in the early embryo stage that trigger aging, rendering us immortal—but not invulnerable. We do not know if such techniques can be developed and made safe, but some scientists think it is possible.

Hydra, freshwater members of the coral and sea jellies phylum are immoral. Twenty-five percent of a*Hydra's* body is composed of stem cells with the capacity for indefinite self-renewal [21,22]. Can we do what *Hydra* do? Can we halt cell senescence and aging with the goal of extending the morphostasis phase of development in humans? *Hydra* are composed of around 50,000 cells; we are composed of trillions of cells. *Hydra* have no organs; we have over 82 organs if we include skin, muscles, and the interstitium [20th edition of *Gray's Anatomy*]. *Hydra* produce clones primarily by budding. When food and freshwater are abundant, *Hydra* populations explode. When food or freshwater are scarce, populations become locally extinct[23,24].

Our population is exploding. That was not always the case. For 10,000 years, human populations remained small (Fig. 2). Then, like *Hydra* under ideal conditions, human populations exploded exponentially with the dawning of the industrial age, not because we started reproducing like rabbits, but because we stopped dying like flies. In 1950, 8% of the US population was 65+ years of age. By 2000, the aging population had increased to 12.4%. By 2050, the aging population will likely exceed 22% (https://www.statista.com/statistics/457822/). Once a rarity, living into the 90s and even 100s is the new norm. Are we the next innovation to carry DNA Eve's progeny into the future? Or are we a cancerous tumor leading to Earth's next mass extinction event.

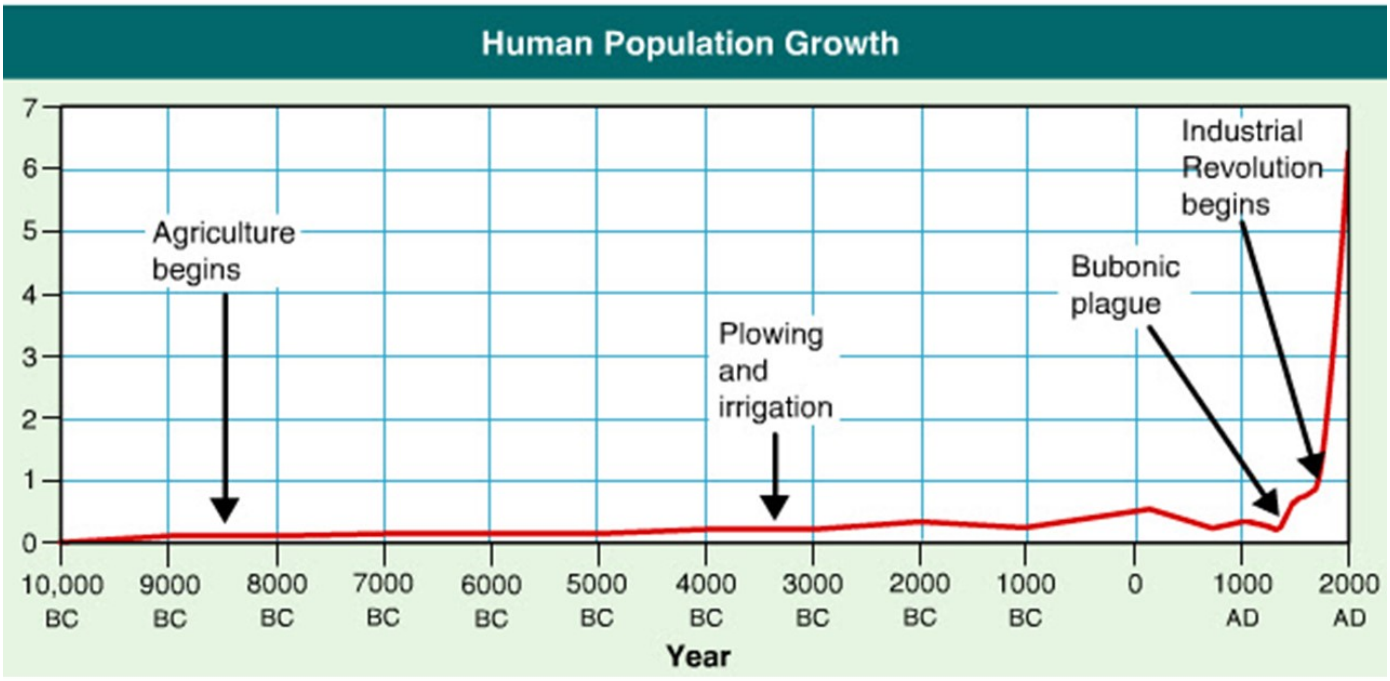

Figure 2. Human population growth over 10,000 years. The Creative Commons Attribution License permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (https://socratic.org/questions/throughout-most-of-human-history-did-human-population-size-skyrocket-remain-at-c).

The International Anthropocene Working Group recently established 16 July 1945 as the starting point of the Anthropocene epoch. Since 1945, the rate of extinction among multicellular plants and animals has risen exponentially along with our exponential population growth. Will we survive the next million years? Time will tell.

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