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Mechanisms of Aging from a Genetic, Molecular and Lifestyle Perspective

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Introduction

Before diving deeper into the subject of anti-aging, it is important to make a couple primary distinctions regarding vocabulary. Life expectancy is the average amount of years an organism is expected to live in their environment. Lifespan is the maximum amount of years an organism can live up to [1]. The two ideas can be thought of in tangent with each other, since life expectancy is really just the average lifespan. Finally, longevity is the ability to survive past the average life expectancy of the population [2]. This is a highly sought after trait seen in animals such as the Galapagos tortoises, bristlecone pines or the immortal jellyfish [3]. The question behind the biological mechanisms that allow for such longevity in these organisms have been a topic of scientific inquiry for centuries now.

Historically, humans have constantly been in search of methods to improve their life spans. This can be seen in old fables about the alchemists, the elixir of life or quests in search of the philosopher's stone. To a certain extent, ways of improving life span have been found, not from exploring alchemy but by making lifestyle changes in nutrition, and improving sanitation and healthcare. Across the world, the average life expectancy of every country, no matter developed or developing, has improved over 2 to 3 times between 1748 to 2019 (Fig. 1) The numbers have exponentially exploded following the post-war period of 1950s, showing that a peaceful environment certainly allows for a longer life span. However, the varied levels of life expectancies across different developing countries showcases other factors that play an even larger role in longevity. An example is the lifestyle of a nation, dictated by their unique cultural backgrounds. The consumption of rice and smaller-portioned meals in Japan is vastly different from the stereotypical American meal. Other factors might include the genetic factors determined by one's race or heredity, epigenetic factors attained throughout one's lifetime, and even mental factors such as depression or bipolarism.

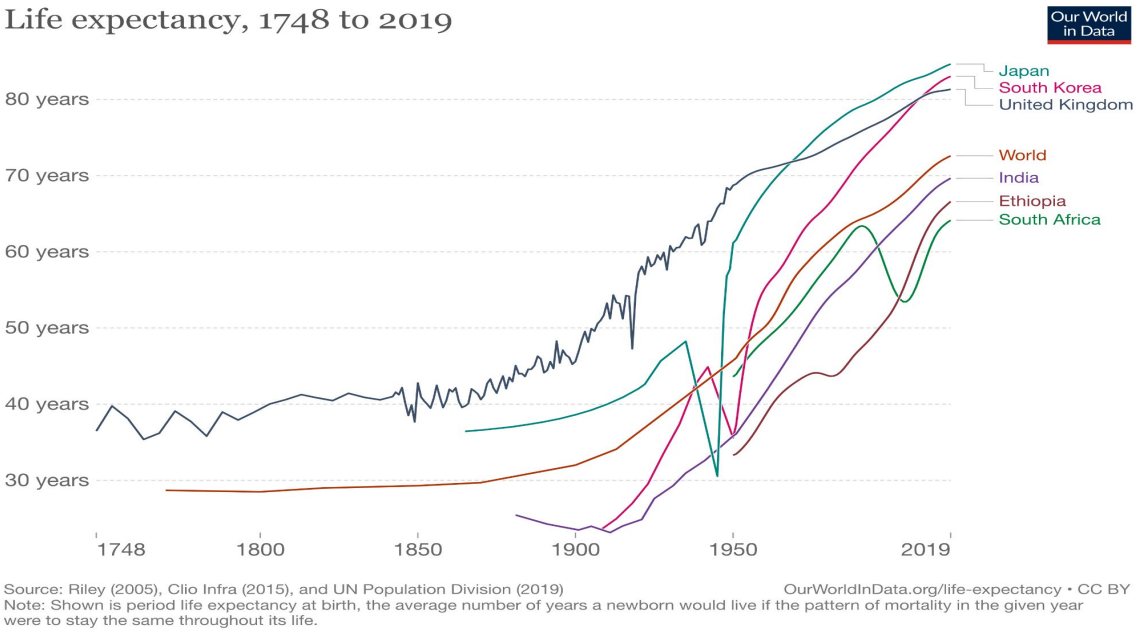


Figure 1. The average life expectancy of a newborn in a given year if the pattern of mortality were to stay the same throughout its life from 1748-2019 [4, 5, 6].

In the next few sections, I will first focus on discussing the scientific basis of aging, as well as animal species who are especially adept at preventing aging by examining the genetic and molecular basis of longevity, generating comparisons between different members of our species or across different species. We will approach the subject by examining the two extremes of aging, the model organisms that have a notable short life span, such as insects, and long-living ones like whales or tortoises. A detailed examination of biochemical and cellular pathways will also be conducted. Next, we will go back to the topic of different life expectancies around the world, and examine how diet, exercise or culture can influence a nation's average life expectancy. Finally, a brief examination of mental causes and the psychology of longevity will also be discussed. The paper will be capped off with takeaways, future directions, and other promising areas of investigation in the ultimate goal of achieving mammalian immortality.

Discussion

What is Aging?

As elegantly stated by the *Evolutionary Biology of Aging*, aging can be understood as: "*a persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration*" [7]. This is the standard definition of aging, accepted across the board historically [8, 9, 10, 11]. Aging is a collection of physiological changes, such as cell death or mutations that slowly causes an organism to enter senescence, or the state where cells deteriorate quicker then they regenerate and when an organism truly starts "dying". The variations of when that death actually occurs between animals is what makes aging so interesting to gerontologists around the world, and what makes gerontology so interesting.

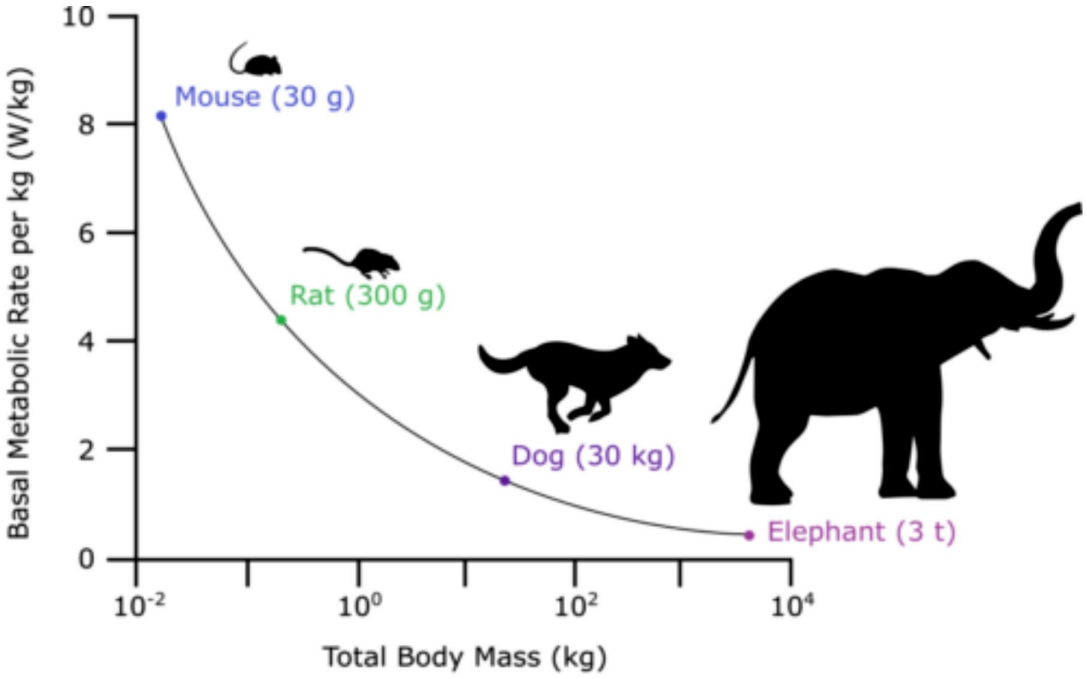
Longevity in Non-Human Species

Prior to examining the basis of longevity in human models, it would be wise to look into other animal species first. Specifically, through an examination of animals on different points of the longevity spectrum: those with extremely short life spans, those with extremely long ones, and those who lie somewhere in between. Since all organisms descended from a universal common ancestor [12], what exactly causes the diverse variance of life spans we observe in the animal kingdom? Why has natural selection favored these variances? How have scientists understood life span in different animals?

Currently, the best predictor of animal longevity is body mass. Holistically, the size of an animal seems to be directly proportional to the length of its lifespan [13, 14]. Take elephants for instance. They are massive creatures with body masses up to 6,350 kilograms and are capable of living up to 60-70 years. On the other hand, mayflies from the order ephemeroptera, meaning "short-lived" in Greek, are a mere 2.7 milligrams in weight, and have an average life expectancy of 1.6 days for males and 2.0 days for females [15,16]. This makes sense logically, the larger an organism is, the longer it takes for them to grow to that size. The smaller an organism is, the more likely it is for them to be the prey instead of the predator. Therefore, instead of favoring longer lifespans, smaller organisms favor shorter ones but have more offsprings.

There do exist exceptions to this general rule of thumb, but these exceptions usually have their own way of adapting to their environment to get around size-dependent natural selection. Turtles, who can live up to a few decades, have the unique ability of using their shells as shelter to protect them from predators. Birds, who live a relatively long life compared to their size, are able to fly to escape any land predators. Of course there are even further exceptions to the general rule of size-dependent longevity, most of which exemplify the role the environment plays in natural selection. However, this theory provides a springboard for other understandings of aging in animal species.

Bioenergetics and thermodynamics are another favorable way of explaining the variance of lifespans. Commonly called the "rate-of-living" theory, it can be expressed simply as: the faster one lives (higher energy expenditure and metabolic rate), the more wear and tear there is, thus leading to a lower lifespan [18]. A useful analogy is with machines: a machine that runs quickly also wears down quicker. Small mammals like mice have a high metabolic rate and live a quick life, constantly scurrying around from place to place, resulting in a lifespan of only a few years. Large mammals, like elephants on the other hand have a lower metabolic rate proportional to their body mass (fig. 2). This relatively lower metabolic rate to their body mass indicates less stress on cells and other pathways, allowing for a longer life in return.



Metabolic rate per unit mass vs. total body mass for different species. Graph demonstrating the respiration rate per kilogram of different species ("mouse-to-elephant curve"). Adapted from Singer 2004. Icons made by Freepik from www.flaticon.com.

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Figure 2. Metabolic rate per unit mass vs. total body mass for different species. A larger body mass correlates with a lower basal metabolic rate per kg, which in turn correlated to a longer life span. [17]

Animals employ a wide range of tactics on the molecular level in order to counteract the effects of aging. All of which are interesting to examine in order to derive possible human applications. For instance, the naked mole rat, Heterocephalus glaber, has an unusually accurate ribosome as compared to other mammals like mice or humans [19]. This greater fidelity allows for less errors and mutations in the translation process and gives naked mole rats a greater resistance to tumorigenesis. In addition to accuracy, scientists have also found that proteins translated from the naked mole rat ribosome are more stable due to more ubiquitous chaperone proteins that assist with secondary structure formation, as well as more effective proteasomes that break down and dispose of defective proteins [19,20,21,22]. The combination of these factors contributes to the naked mole-rat's unusually long life span.

In another animal example, lobsters or Homarus americanus are organisms who seemingly never go into senescence. That is, they do not reach a point where their cells start deteriorating at old age. On the contrary, lobsters are able to regenerate claws and continue molting throughout their lifetime. This characteristic can be attributed to their ubiquitous telomerase even in adulthood, which repairs the important telomere caps that protect DNA, effectively regenerating from any damages [19,23,24]. Telomerase plays a major role in the lobster's possible 140 year old life span, which can be hypothetically even higher since lobsters die naturally not of age, but because of a lack of energy to continue molting and forming a larger exoskeleton. In general, responses to aging in various animal species mainly include a vigorous DNA or cellular repair system, which allows for fixes before tumors or other fatal mutations.

Humans

Humans are particularly interesting, in which they present a vastly different exception from other animal species in terms of aging. Digressing from the mass definition, the average american male is around 200 pounds, while

the average male elephant can weigh up to 15,000 pounds [25,26]. By the same token, humans also have a way higher basal metabolic rate per kg of body mass as compared to elephants[17] (fig. 2). This 1 to 83.33 weight ratio and higher wear and tear would logically infer a lower lifespan in humans. Instead, the average life expectancy for a male child born in the United States is 74.5 years while the maximum life expectancy of an elephant is around 70 years old. Not only do humans outlive elephants, our life expectancy has been constantly on the rise since the industrial revolution, increasing by 6 years within the past two decades [27]. The use of proper sanitation techniques, as introduced by Florence Nightingale and Sir Edwin Chadwick and innovations in medicine like penicillin or surgery are unique and a driving factor behind our ever-increasing longevity. However, these are not the only factors responsible, since aging is the effect of a myriad of biological components working together. Not only are there genetic and biochemical factors, but also lifestyle, cultural, or even mental issues that could be considered to fill a comprehensive understanding of aging.

Genetic Basis of Longevity

Does having a supercentenarian (those who reach the age of 110) relative increase your chances of living to a similar age? The answer seems to be yes, and plentiful research in recent years has attempted to solidify the bridge between longevity and genetics (ref 28). There have been families full of centenarians [29] as well as studies that show an increased rate of survival for those with long living siblings [30,31]. As evidenced by the studies, the strong connection between genetics and longevity allowed scientists to hypothesize that there was a genetic variant, possibly some gene that conferred a sort of resistance to diseases that affect longevity in these centenarians. In a genome-wide association study (GWAS) led by Paola Sebastiani, 801 centenarians and 914 healthy controls were studied for specific genetic changes called single-nucleotide polymorphisms (SNPs) [32]. The presence of SNPs have a large, collective effect on genes. Like a cause and effect line, SNPs affect genes, which could either express a resistance or acceleration of certain diseases, directly affecting life span. Through a genetic risk model constructed from 130 selected genes, there was a better understanding of the link between genes and their effects on Alzheimer's disease or coronary artery disease, both leading causes of death in the USA. Two notable genes of study were *LMNA* and *WRN*, which both had variants who could accelerate aging and variants who could increase life span. The results of the data conclude that longevity might only be the beneficial genes outweighing the disease-related ones, like a scale that can tip towards both sides.

Further research led by Sebastiani attempts to utilize certain SNPs to act as predictors for longevity [32]. Specifically, the use of the SNP rs2075650, a part of the *TOMM40/APOE* gene commonly associated with exceptional longevity in centenarians. However, further studies still need to be conducted to improve the accuracy of the predictions.

In theory, long-living families should harbor multiple favorable SNPs or longevity-benefiting genes. For now, it does seem like longevity is primarily genetic, as having a long-living first relative also confers a longer lifespan [33, 34]. However, as clearly suggested by twin studies by Herskind, genetics only account for around 25% of a person's chances of living to 85 years old [35] . The role of genes is limited when compared to other factors, such as environmental ones.

Molecular Basis of Longevity

Aside from genetics, recent research has elucidated various biological causes of aging, shedding light on different biological pathways related to the complex longevity and aging phenotypes. One of the most notable advances is the discovery of the role of telomeres with aging. Telomeres are protective caps on the ends of DNA that protect eukaryotic chromosomes from degradation and harm. However, telomeres also shorten overtime with normal cellular replication. Therefore, telomere length is an important factor of longevity and a short enough telomere length could lead to cell senescence or cell death [36]. Whittemore et al. found in a study of 8

vastly different animals that the rate of telomere shortening strongly predicted the animal's life span; those with slower telomere shortening rates lived for longer and vice versa [37]. They also found other differing factors such as the original, starting telomere length. As related to the bioenergetics definition of aging, since telomeres are protective caps, external stresses and a generally fast-paced way of living have a wear and tear effect. Ultimately, leading to death by aging. Recent studies have identified new biomarkers – certain proteins – that could identify potential telomere dysfunction [38,39,40]. It remains optimistic to find a solution to longevity based on the study of telomeres.

The Sirtuin (SIRT) family, a collection of nicotinamide dinucleotide (NAD+)-dependent deacylases play a major role in protecting genome integrity through repairs or helping maintain chromatin structure. They are known to regulate various processes that prevent diseases and reverse aging [41,42,43]. Interest in this collection of molecules grew after studies on various yeast, worm and mammal SIRTs, which showed various functions in improving longevity. For instance, the seven sirtuins in mammals are each localized in different organelles in the cell and play different roles in aging prevention (Table 1). The role of Sirtuins in the aging process is still under debate. Some studies have shown that increased levels of SIRTs were successful at increasing the lifespan of budding yeast, worms, fruit flies and mice [44,45,46,47]. On the other hand, several studies have also examined the controversy behind Sirtuins. Some studies have shown that SIR2 in budding yeasts don't actually play a role in the cellular senescence pathway, rendering the role of Sirtuins in longevity null [48]. Additionally, some issues regarding the original lifespan extension studies of sirtuin overexpression also came up. In general, these debates are welcome for a better understanding of the biological pathways of aging.

Table 1. Properties and functions of Sirtuins related to senescence and aging [41]

Sirtuin		Cellular localization	Activity	Functions in cellular senescence and aging
Yeast	SIR2	Nucleus	Deacetylase	DNA damage repair
				Replicative lifespan extension
				Cell cycle arrest
C. elegans	sir-2.1	Nucleus and cytoplasm	Deacetylase	Lifespan extension
	sir-2.2	Mitochondria	Unknown	Lifespan extension
	sir-2.3	Mitochondria	Unknown	Lifespan extension
	sir-2.4	Nucleus	Unknown	Stress resistance
Drosophila	Sirt1 (dSir2)	Nucleus and cytoplasm	Deacetylase	Lifespan extension
	Sirt4	Mitochondria	Unknown	Lifespan extension
Mammal	SIRT1	Nucleus and cytoplasm	Deacetylase	Lifespan extension
			ADP-ribosyl-transferase	DNA repair
				Cell cycle arrest
				Cellular senescence
	SIRT2	Cytoplasm	Deacetylase	Cell cycle regulation
	SIRT3	Mitochondria	Deacetylase	Mitochondrial function
				Oxidative stress
				Centenarian-linked SNPs
	SIRT4	Mitochondria	ADP-ribosyl-transferase	Fatty acid oxidation
			Deacetylase	Apoptosis
	SIRT5	Mitochondria	Demalonylase	Fatty acid oxidation
			Desuccinylase	Oxidative stress
			Deacetylase	
	SIRT6	Nucleus (chromatin)	ADP-ribosyl-transferase	Lifespan extension
			Deacetylase	DNA repair
			Deacetylase	Genome stability
				Telomere maintenance
	SIRT7	Nucleolus	Deacetylase	Epigenetic regulation

In addition to telomeres and Sirtuins, further research has also elucidated the role of the insulin-like growth factor 1 (IGF-1) pathway in longevity regulation. This conclusion came from research that showed that insulin resistance increases and sensitivity decreases due to aging, which could lead to complications such as hypertension, atherosclerosis or obesity [48]. IGF-1 are hormones in blood that regulate the effects of growth hormone on the body. It seems to have a varied role in aging. In studies on a cohort of centenarians, although IGF-1 had protective factors and could function in neuronal protection, fetal/skeletal development and promoting insulin-like effects, it also led to increased tumor activity due to its proliferative nature. In mice studies, the down regulation of IGF-1 led to improved longevity [49]. In humans however, study results remain split. Some, like studies by Paolisso et al. attribute an increased plasma IGF-1 to the exceptional lifespan of centenarians [50]. On the other hand, others suggest lower levels of plasma IGF-1 to be more present in long living humans [51]. Generally in yeast and mice models, it seems like disruptions to the IGF-1 pathway by injury or mutations lead to an increased lifespan. However, there have been trouble looking for the same effects in humans as compared to these model organisms. Some scientists attribute this to the varied ethnicities and gender, which further adds to the complexity of the IGF-1 pathway [52].

In the past decades, scientists have discovered even more pathways that contribute to the molecular basis of aging. For instance, chromatin remodeling, transcriptional and posttranscriptional regulation, epigenetics, mitochondrial homeostatic etc. As these ideas continue to be debated and polished and a full biological picture is painted to understand the complex system that is aging, solid evidence has already concreted the effects of a proper lifestyle on human longevity.

Effects of Lifestyle on Longevity

In the modern human environment, many of the usual environmental stresses, such as predation, hunger, thirst, and mainly a struggle for survival are mitigated by our blooming metropolises and rising standards of living. However, ages still vary within our species. In a cohort of nonagenarians and centenarians, factors like education, income and professions varied greatly. The one thing that did not vary, however, were their lifestyle choices. There are many aspects of one's lifestyle that could influence one's life span. The single most important one is their living environment: what kind of environmental stresses are placed on an organism?

Environmental stresses begin the moment one is born. A poor environment could lead to a greater susceptibility to disease or other epigenetic factors. For instance, long term exposure to fine Particulate Matter (PM2.5 or air pollution could lead to the development of cardiovascular and respiratory diseases [53]. On the molecular level, chronic exposure to pollutants in the air could also lead to genomic instability, telomere weakness and mitochondrial dysfunction [54,55]. In addition to air pollution, factors like water pollution and soil pollution also play a major role. Aside from toxins, general geographic features such as atmospheric pressure, temperature, relative moisture and duration of sunshine. The effects of these features were most prominent in older cohorts above the age of 65. In a study of the connection between meteorological factors and acute myocardial infarction (AMI), it was found that occurrences of AMI were more common in colder temperatures, and with every cold day, the risk for AMI increased by another 5% [56,57]. Additionally, it was observed that men suffered a greater risk and effect from meteorological factors [56,58]. Aside from the cold, extreme heat events also raised the risk of AMI among different subgroups. However, results ranged between genders, ages as well as past illnesses histories [59]

Another environmental stress ties in with the diet and nutrition one consumes. The food one eats varies between culture to culture. For example, some cultures might have red meat as a staple source of protein while others might prefer fish. The connection between food and health has only been confounded by commercial production of food. The consumption of junk food can lead to various health problems like childhood obesity, cardiovascular issues, diabetes or even cancer [60]. Fortunately, some diets and cuisines do increase the chances of living to a certain age. For instance, the Mediterranean diet, consisting of tons of plant-based goods, fish, moderate red meat consumption, and nuts and olive oil as main sources of lipids. The benefits of this diet are plentiful: lower risk of myocardial infarction, stroke, heart failure, disability etc [61]. In other studies, green tea *Camellia sinensis* as well as moderate consumption of wine was shown to have similar anti-aging effects on the body [62,63]. On the flip side, coffee was shown to have a negative, aggravating effect on the body [64]. In general, the nutritional evidence does point to countries like Italy and Japan as areas of longevity, and this inference is supported by the fact that Japan and Italy are ranked 2nd and 6th respectively for their country's expected lifespan [65]. It is important to know that it is not necessary to travel to another country just to live longer. In theory, a carefully monitored diet for all the essential vitamins and minerals, and ensuring an adequate consumption of each would also be beneficial.

Here it is also worthy to point out another form of dieting: calorie restriction. A human diet would be considerably restricted, only intaking the essential nutrients once or twice throughout the day. Although this technique has been shown to be viable in various short lived species such as the roundworm *Caenorhabditis elegans,* prolonging life spans up to 45% [66]. Mammalian studies have also been conducted to a certain success,

but recent research has shown unintended damage to other parts of the body and this remains a dangerous form of improving longevity [67,68]

In addition to a well rounded diet, physical activity is another commonly accepted way of increasing longevity. Similar to eating well, physical activity has many of the similar health benefits and decreases predispositions to diseases. Cohort studies suggest that regular physical activity could increase one's life span anywhere from 0.4 to 6.9 years [69]. Another study of cardiorespiratory fitness showed a positive correlation between general fitness and survival rates, presumably allowing the body to pump blood more efficiently and aiding in other bodily functions [70,71].

Finally, an important consideration in the modern age is the effect of one's mental health on longevity. Unfortunately, suicide rates, depression, and stress are common in our world. A recent study from the Finnish institute of technology showed that being under heavy stress reduces one's life expectancy by 2.8 years [72]. On a smaller, molecular level, it was shown that stress increases oxidative pressure, which reduces telomerase activity and has an effect on telomeres [73]. In general, staying happy and relaxed is the agreed upon solution to this unfortunate situation. The less external stress one puts on their body, the longer their body will hold up over time.

Conclusion

Surprisingly, research has found a longevity associated genetic marker in 15% of control subjects. This suggests that these controls also have the potential to become centenarians or even supercentenarians [32]. Through a perfect, goldilocks-like control of different environmental factors, it is possible to skew one's life expectancy and healthily age. However, research and debate still remains prominent in gerontology since the ultimate quest for conquering death is a never-ending one. It is entirely possible that average life spans will completely shift within the next few decades, and it is an exciting field of study that is sure to affect everyone on the planet.

Acknowledgments

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