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Extending Human Life: Progress and Implications

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Abstract

Objective: To gain an overview of progress scientists in different disciplines have made in understanding factors that influence senescence and extending life spans.

Method: Review of the literature.

Results: Clinical trials involving stem cells are showing effectiveness to repair and rejuvenate tissue. Using adult stem cells, different human organs are being grown in laboratories and animals. Genes have been identified that correlate to cell maintenance and basic metabolism as primary genetic factors affecting the variability of the aging phenotype.

Discussion: Senescence related research suggests that life expectancy will continue to increase because of the ability to prevent disease. As the average life span increases, the economic and social impact will be enormous. For example, the workplace will deal with changes of limited upward mobility for the young. Workplace managers will have to manage employees across a broad age range. Healthcare organizations and third parties will be required to make major changes to accommodate a broad range of healthcare needs. Macro and micro economic behaviors will see significant changes as societies needs grow but opportunities will be limited due to the number of people still living.

BACKGROUND

The purpose of this article is to explore the current state of slowing senescence. Factors affecting the slowing of senescence operate in a global environment and are themselves impacted by efforts in healthcare that while treating/managing diseases extend life. These factors are discussed as they are opening immense scientific and business opportunities.

Regenerative medicine is defined by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) at National Institute of Health (1) as: "Regenerative medicine is a broad field that includes tissue engineering but also incorporates research on self-healing – where the body uses its own systems, sometimes with help from foreign biological material to recreate cells and rebuild tissues and organs." The interchangeable terms "tissue engineering" and "regenerative medicine" aspire to cure diseases and conditions rather than developing treatments for diseases (1). The field of biomaterials development is the underpinning of regenerative medicine. The field consists of combining scaffolds, cells, and biologically active molecules into functional tissues. Examples of successfully engineered tissues include artificial skin and cartilage, lab grown blood vessels and cushions found between spinal discs. It should be mentioned that many of these developments have been approved by the FDA (1).

Regenerative medicine scientists are envisioning a world where it is a common place to transplant a heart, pancreas, liver or a kidney grown from the patient's own cells. This practice of medicine will become as common as joint replacements are today. If senescence is slowed, we could see a world where 100 year old people are playing tennis or actively participating in other arduous sports. Science has not yet arrived at significantly decelerating senescence however, slowing it down is within grasp as medical scientists have begun dissecting the aging process.

The world has seen average life spans increase over the past 100 years primarily due to advances in disease treatment, public health practices, healthy nutrition and sanitation. United Nations data show it is a reasonable assumption that life expectancy will continue to rise as effective treatment/cures of diseases are developed (Figure 1). This assumption may be augmented when future increases in the average life span are due to organs grown from the patients' own stem cells. As we live longer, individuals will want to maintain a quality of life that fosters a driving force for the development of anti- senescence drugs and a host of treatment methodologies. It should be noted that some anti-senescence drugs already exist (2). Today gene and cell therapy show promise in not only extending life but also the quality of life by addressing the underlying causes of cardiovascular, and neurological diseases as well as urinary incontinence. (3)

The advances in healthcare over the last 100 years are evident and abundant. Significant innovations in the treatment and management of disease and conditions have focused on preventing, managing and curing disease through improvements in antibiotics, vaccines, cancer treatments, HIV/AIDS, hepatitis, and diabetes to mention a few. Advances in public health aimed at sanitation, air and water quality, mosquito abatement, vaccinations, and education regarding addictions, nutrition, and

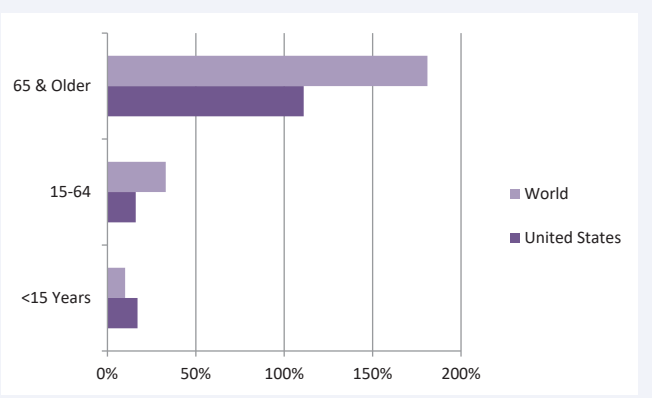

Figure 1 Estimated Percent Change in Population, 2010 to 2050, by Age in the World and U.S.

exercise have all contributed to improved health and have had a positive bearing on life expectancy. While these efforts are well underway in developed countries, there are significant benefits to be realized in developing countries where life expectancy lags that in developed countries.

Current Healthcare Efforts to Slow Senescence

Medical scientists are enthusiastic about the possibility of extending average life spans to the unimaginable 130 years. This will be made possible in the future because as organs fail they can be repaired or replaced. Organ replacement, cell regeneration, and gene therapy coupled with anti- senescence drugs will make centenarians a common feature in decades to come (Figures 2, 3).

There is a plethora of research literature on stem cell clinical trials showing effectiveness, while other trials hold promise (4). Regenerative therapies pursue supplementation of this repair process by using stem cells obtained from existing body cells or from frozen placentas. Scientists working in the field of regenerative medicine are conducting clinical trials with stem cells and showing some encouraging results. For example, nerve cells grown from human embryonic stem cells and then transplanted into rats that possess the comparable disease of Parkinson's in humans start to grow and multiply releasing dopamine which is what people and rats are lacking (5). A trial at the University of Cambridge treated a Parkinson's patient using this technique. Another clinical trial in Whales has the aim of examining the efficacy of stem cells to treat stroke related disabilities (6). The future looks hopeful considering the amount of money directed towards stem cell research. In the United States, the National Institutes of Health funded $1.3 billion in stem cell research in 2013 and will allocate almost $1.5 billion in 2016. (1). The number of active stem cell researchers globally has grown from 4,500 in in 2002 to close to 100,000 in 2012 (7).

Attempts to slow senescence go beyond the potential that appear in stem cell research and include attempts such as parabiosis (a technique in which researchers sew a young mouse and an old mouse together so that they share a circulatory system). The young mouse's blood seems to rejuvenate the old mouse, regenerating its wasting muscles and restoring its cognitive abilities (8). Efforts to grow organs are under way. For example, researchers at the University of California, Davis are in the very early stages of using adult stem cells to grow human organs. What is interesting about this research is that these human organs are being grown inside pigs (9). The endeavor to solve the global donor-organ shortage has created embryos that have both human and pig cells. By injecting human stem cells into pig embryos, human-pig embryos known as chimeras develop. The UC-D researchers expect the human stem cells will benefit from the genetic niche in the pig embryo and the subsequent fetus will grow a human pancreas.

Longevity has long been recognized to run in certain families begging the question; what role do genes play in longevity? Recently, Italian scientists have shown that about 25% of the deviation in human longevity is because of genetic factors. Their studies have identified the genes that are correlated to cell maintenance and basic metabolism as the primary genetic factors affecting the variability of the aging phenotype. Scientists have begun investigating the role of genes with the aim of using modern gene-editing techniques to modulate the DNA of individuals who will benefit from such modulation (10).

Studies on calorie restriction and the variability of nutrient-sensing signaling genes show an ipocaloric diet does modify the life span through an efficient maintenance of the cell (10). In some animal studies, calorie restriction (CR) has been associated with a reduced risk of cancer and heart disease while slowing the

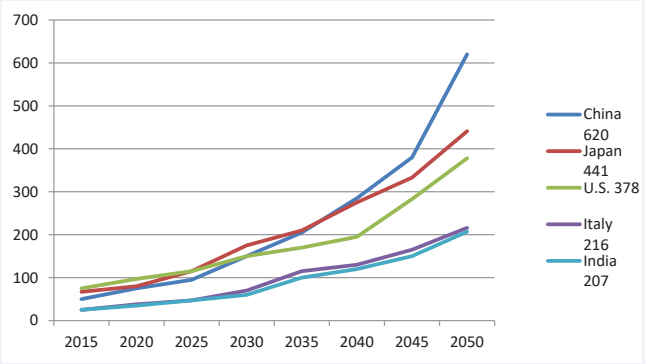

Figure 2 Number of Persons Who Are 100 Years or Older.

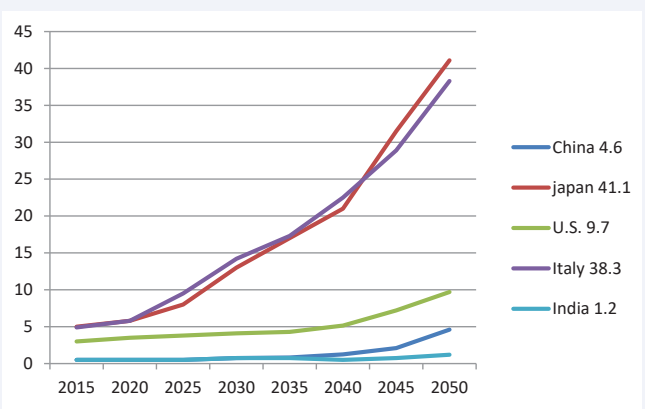

Figure 3 Number of Persons Aged 100 and Older per 10,000.

degeneration of nerves, hence extending life (11). An example is 45 year old Michael Rae of the SENS Research Foundation who eats 1,900 calories a day. That is 600 calories less than the recommended number. Mr. Rae believes that if the results found in rodents hold true for humans CR could extend his life by 7-15 years. CR dieters report blood pressures similar to those of young children and arteries without blockage. In short, epigenetic studies show when epigenetic adaptations are made, both genetic make-up and life style demonstrate significant sensitivity to the aging process and serve as indicators for the rate and quality of aging (10).

For the past 25 years it has been known that stimulating changes in metabolism and in particular the daf-2 and daf-16 gene in roundworms slow the aging process and double the roundworms life span (12). The corresponding genes in humans are responsible for the cell-surface receptors for insulin and insulin-like growth factor 1 and are hormones with central metabolic roles. The equivalent of daf-2 in humans appears to be turned on by CR. Variants of daf-16 have been found in humans with long lives (13).

CR appears to deactivate mTOR, a protein that facilitates signals from growth hormones to the segments of the cell involved in protein synthesis. The role mTOR plays is regulating the cell's metabolism, growth and division, and prevents the breakdown of cells that have been damaged. It has been observed that when food is plentiful mTOR stimulates cell growth and division. In animals where CR works well, mTOR appears to switch cells from a system of growth to one of concentrating on their own repair (14). When focusing on their repair damage to the cells accumulates slower translating into aging less. Drugs such as metformin and rapamycin appear to achieve the same effect. Reducing the function of mTOR has been shown to extend the life in yeast, worms and flies (14). However, these current efforts remain speculative. CR is unproven to extend human life but it has demonstrated a positive effect in animals. While this is an exciting finding, consideration must be given to the role of genetics and pharmacology in the slowing of the aging process. Controlling the environment (e.g. nutrition, housing, and public health) has a longer history than controlling the genetics that trigger the metabolic pathways involved in aging. Treatments intended to control genetics with drugs offer a greater potential to manage and cure diseases/conditions than drugs designed for specific diseases.

Other drugs such as resveratrol have been studied. Initial studies a few years ago were promising as the drug kept mice that ate a rich diet youthful but interest declined when it was shown to be less effective in mice that were not over weight. Today the drug is being studied as a possible Alzheimer's treatment. Thomas von Zglinicki of Newcastle University has found that cells experiencing mitochondrial damage have an arduous time recycling damaged or broken cell material (15). This produces a pro-inflammatory factor of cytokines which cause neighboring cells to senescence and chronic progressive inflammation that is attributed to various age related pathologies.

Research into areas that may have the consequence of slowing senescence is not limited to the clinical laboratory where efforts in areas of stem cell, gene therapy, cell regeneration abound. A plethora of data has been generated in all these areas of research and the quantity of data is growing exponentially. Efforts are underway to mine the data to identify promising areas of further research. For example, at the Insilico Medicine in Stuttgart, Germany, Dr, Alex Zhavoronkov is examining the plethora of published genomic data in an effort to identify the tissue differences between old and young individuals (16). An additional interest is examining the patterns of gene expression in the aging process. This is followed up by mining drug databases searching for molecules that may block the relevant gene expression.

Dr. Eileen Crimmins at the University of Southern California cites calculations that show the total elimination of cardiovascular disease would only add 5.5 years to life expectancy in the United States. Eliminating cancer deaths would add 3.2 years to life expectancy. The reasons for such small advances in the life span are because diseases and conditions compete in the pathophysiology of aging. Over time defending against a large array of diseases becomes more and more difficult. A current study at Newcastle University in Australia has enrolled close to 1,000 subjects who are 85 years old and none of them are free of any pathology. They report an average of 4-5 health problems (17).

DISCUSSION

Increasing the average lifespan has many proponents and just as many dissenters. While it is interesting, and at times fun, to consider the possibilities of people living to 120 years of age or longer, there are two key factors that impact efforts to slow senescence. These factors are funding and technology.

Funding

The improvements in healthcare and technology come at considerable cost. In 1980, for example, healthcare spending accounted for about 8.5% of GDP in the US. It amounts to over 17% of GDP today. Healthcare spending globally is expected to rise from $7.83 trillion in 2013 to $18.3 Trillion in 2040 (18).

New medicines are more costly to develop and pass through rigorous testing to meet regulatory standards not only in the US but in other countries as well. Then, too, treatment advances in healthcare are geared to making treatments more effective not necessarily less expensive. An example is the MRI which is very expensive but markedly improves the accuracy, effectiveness and safety to the diagnosis and treatment. Underpinning the advancement in treatment modalities is the basic research that leads to new medicines, technology, devices, and treatment protocols.

Funding for research comes from many sources including drug companies, grants from governments and foundations, private sources, universities and other organizations. While funding of efforts to improve the ability to cure/treat diseases it is likely to continue, it is less clear that funding specifically directed at slowing senescence will accelerate because aging happens to everyone. Consequently, it has not been considered a condition in need of treatment. This perspective prevents oversight agencies that allow drugs to be sold to consider senescence a condition that merits treatment. Unless aging is considered as a condition

meriting treatment, drugs that specifically slow senescence cannot obtain regulatory approval. If this opinion were to change, the research activity would likely increase considerably.

Technology

For the purposes of this paper, we use the term technology to be inclusive of information technology, informatics, medical devices, nanotechnology, artificial intelligence, mobile technology, methods and instruments for analysis, and medical procedures. Information technology (IT) is relatively new in the field of healthcare appearing on the scene in the IT boom of the early 90's and has had a significant impact on the delivery and improvements in healthcare (19). Many of the IT realizations have been ascertained in administration (centralization and sharing of patient data) and finance (insurance, billing, and reports to health care agencies including Medicare and Medicaid). These IT advances have improved the efficiency and effectiveness of healthcare services (20). Advances in information technology will continue and are needed to improve the efficiency of providing healthcare. A more important underpinning for advances in the treatment and cure of diseases occurs in a number of important areas of medical technology including:

1. Advances in methods of analysis (e.g. MRI, CT & PET Scans).
2. Advances in laboratory instrumentation that allows research to peer into diseases and cures at the molecular level.
3. Advances in devices that have a dramatic impact on healthcare including intraocular devices, ablation systems, left ventricular support systems and a meniscal unicompartmental knee system as listed on the FDA Post Approvals List. Printers (3D) have reduced the cost of creating artificial joints and other devices to improve the quality of life (Medicalphysicsweb).
4. Advances in surgical treatments and procedures including orthoscopic surgery, neurosurgery, etc.

The speed of advances in areas of regenerative medicine mentioned earlier will depend on advances in myriad areas of technology.

The Impact

Whether aging is considered a condition that merits treatment and therefore attracts specific funding to slow senescence, the relentless search for disease prevention, cures, and treatments will continue driven by demand from consumers and their insurers who desire more effective and less costly cures/treatments of diseases. The unintended consequence of these efforts will be to slow senescence. Evidence supporting the unintended consequence is unequivocal. For example, while centenarians make up a small share of the world's population, there are 4 times as many in 2015 compared to 1990 (21). The United Nations estimates that the growth in centenarians wills accelerate across the globe to over 3.5 million over the next 30 years with China, Japan, Italy, and India having the greatest number of centenarians (21). In the US, the population 65 and older is projected to more than double to over 80 million in 2050 and globally that population is expected to triple to 1.5 billion by 2015 (22). It is insightful to note that not only are the numbers of those over 65 increasing, but the percentage of the world population over 65 is also increasing due to better healthcare but also to lower fertility rates particularly in the middle class (22). As a result, the dependency ratio (the size of the non-working age group – children and elderly) is projected to rise from 59 for every 100 Americans to 72 in 2050. The biggest contributor is the growth in dependency ratio in those over 65. (21). These trends coupled with improvements/advances in healthcare that extend life have enormous implications that are discussed below:

Healthcare

What we consider chronic diseases today will take on a new meaning and how these diseases are treated will have staid implications as populations throughout the world age. Physicians will have to be trained to manage patients with multiple episodes of a chronic disease and the ensuing outcomes. New diseases and conditions will emerge that will require treatments that are effective in both a young child and a 120 year old person. Drugs used over long periods of time may lose their effectiveness and alternative drugs will be required while attending to drug interactions. The clinical laboratory may be required to establish reference ranges for different age groups in addition to introducing numerous new tests and many of those will be based in the molecular diagnostics section of the laboratory. Reporting an elevated biomarker may not be sufficient as clinicians may require information on the history of that biomarker in conjunction with other biomarkers and genetic testing. With an expanded lifespan, the clinical laboratory will be required to become even more complex and sophisticated than one can imagine. The Imaging department will face demands similar to those of the clinical laboratory and it is not unreasonable to imagine some over lapping of the two disciplines will be necessary to understand future diseases and conditions. Disciplines such as physical and occupational therapy will see a cadre of demands whose treatments will have to be tailored more than they are today. It is reasonable to imagine muscles that weaken at one age do so again at another age requiring different treatment regimes. Or patients who are treated for one disease after having been treated for another one earlier such as heart surgery followed at a later time by an emboli or aneurism.

Healthcare facilities will also be required to make major adjustments. Nursing homes may be caring for a 60 year old person who did not have the financial resources, information, or motivation to seek treatments as well as a 120 year old person. The same holds true for hospice care. The meaning of a DNR (do not resuscitate) may take on a new meaning as well as living wills. The legal profession will face new legal challenges with an expanded lifespan by having to draw up new documents and face new legal arguments in all aspects of senescence.

And new healthcare disciplines may emerge requiring innovative educational programs and assimilation into the healthcare industry. All of this will be accompanied by new accreditation standards and ways of delivering healthcare.

Government policy

Third party payers and governments will have to develop new

policies and perhaps set limitations to their healthcare contracts. For example, the number of heart transplants a third party or social programs will pay over a patient's lifetime will become a relevant question as well as the number of times a contract will cover other multiple treatments. We face these issues today as we address the cost of healthcare considering the cost for healthcare in 2013 for those 65 and over are estimated to be $21 trillion over a 20 year horizon. That amount is expected to grow to $50 trillion for those over 65 for the same time horizon in 2050 (23). Ultimately the costs of new developments are born by consumers and their insurers. Whether either of those payers is willing to continue to spend increasing amounts for new and more effective treatments remains to be seen as policymakers face the question of how to allocate scare resources across multiple and conflicting priorities.

In light of ever growing dependency ratios, societies are facing a situation where the working class cannot support the growing aging population. Solutions include extending the age at which people are eligible for government support such as Social Security in the US. European countries have been raising the retirement age and the European Union plans are to link the retirement age to life expectancy (24) Such policies considerations are controversial and involve constituencies with vested interests that are difficult to change (25). The cost of healthcare is likely to conflict with other needs in societies around the globe. These needs include general education, infrastructure, housing, and defense. All of which will require policy adjustments in a societies that lack the ability to reach consensus on competing priorities perhaps delaying difficult decisions to the point of crisis. The need for robust and open dialog about these conflicting priorities is paramount.

Workforce

As people are healthier for longer periods of time, it is likely they can work and will want to work beyond what is considered time to retire, e.g., 65 years. As automation decreases the number of low skill jobs (26), competition for jobs will increase between the older population with experience and skill and the younger generation looking to build a career. Then, too, how will attitudes of employees change if employees that are 60 years apart in age have to work side by side?

Education

As lower paying jobs decline, younger people will need to acquire the skills needed for more skilled work. Typical educational venues such as college with their many fees may not fit the lifestyle or may be too costly for some (27). Education would have to make substantial adjustments in cost and infrastructure as people may delay a college education until later in life. On the opposite end of the age spectrum, people in their 60's may want to return to school to become educated or skilled in a new discipline. Imagine a CPA doing taxes for 80 years, a pharmacist counting pills at a pharmacy or a grocery store checker all working at the same job for many decades. They may view a future enabled by a new skill set.

Other issues:

Psychological issues may explode causing new societal norms. Boredom in many areas of life will likely be a problem. Imagine people who do not have the economic resources to maintain an expected quality of life coupled with societies whose resources are taxed by competing priorities and reduced revenue. Will marriage take on a new definition or will people be happy staying married for 80 to the same person? The cultural issues surrounding the extension of senescence will abound.

CONCLUSIONS

Our research shows that specific efforts to slow senescence will continue albeit there are challenges with funding and regulatory approvals that will impact the speed to results. Advances in technology will also underpin progress in slowing senescence. Our research also substantiates that current and future work with stem cells, genetics, cell regeneration and repair, and a multitude of other areas aimed at curing/treating diseases will have the unintended consequence of slowing senescence. Then, too, the research in these areas will provide valuable information with will contribute to the specific goal of extending life. As these efforts bear fruit, the impact on societies around the globe in areas including healthcare, education, the workplace, and public policy will be enormous. The impact is already being felt and will continue to become more apparent as populations age. It is vitally important that we have robust and open dialog across the global about how we will allocate scarce resources among priorities including healthcare, education, defense, economic growth, and a multitude of societal needs. Equally important is the ability of policy makers to align on processes that facilitate open debate and provide a path to decision while we have options for productive and equitable solutions.

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