MEDICAL BITS FROM YOUR DOCTOR

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"True Happiness is to enjoy the present without anxious dependence upon the Future".

Lucius Annaeus Seneca

"Be tolerant with others and strict with yourself".

Marcus Aurelius

YOUR HEALTH: Longevity – Part I

All Humans wish a long **lifespan** and most importantly, a commensurate **health span**. Of course, the finality of life, is the "great equalizer" of humanity and an intricate part of who we are as a species. Arguably, it's a major daily motivator, as we all wake up ready to "seize the day" and honor *"carpe diem"*.

The aspiration for "*longevity" is so* old, and so much a part of us, that the earliest surviving manuscripts recount mythical long-lived figures. Sumerian mythology written around 4000 BC in rudimentary ancient cuneiform characters, already described Enki, a major God associated with water, wisdom, magic and immortality. And even in my endless Pampas, I heard of Gilgamesh, the legendary king of Uruk, who embarks on a journey to find eternal life. Babylonians later appropriated the epic tale and further explored the theme of immortality and the search for eternal life. Hindu mythology describes the sage Vyasa, as having lived for thousands of years.
And we are all familiar with the Book of Genesis' story of Methuselah, who traces his genealogy back to Adam, is the grandfather of Noah and dies at age 969 in the year of the Great Flood (brought about by Noah's construction of the Ark, and confirming that no good deed shall go unpunished from the earliest days of humanity!).

Over the past few centuries but particularly over the past few decades, our world and health span have been transformed. Before modernity, average life expectancy was 20-30 years and very few humans died from age-related diseases. We face a different reality, as more than 20% of the global population of 9 billion will be older than 60 by 2050, sharply increasing the prevalence of chronic diseases. Fortunately, we have made strides in aging research, with the identification of hundreds of "aging" genes with strong evidence of evolutionary conservation in longevity genetics and the metabolic pathways encoded by them leading to the identification of small molecules able to successfully manipulate some of them.

Hence, my informed patients have been reading and wondering about all the "buzz" and frenzy surrounding "Longevity". Numerous "gurus" provide daily advice through books, articles, podcasts and videos, on how to extend our time on planet Earth. Numerous supplements, monitoring devices and biologic markers are being touted and promoted in that immortal quest for eternity. And since Medicine and Preventive Medicine are very much at the heart of "life extension", we feel the "heat" and responsibility in summarizing some of the science and clarifying some of the "myths" (which you realize are more interminable than life itself).

Let me invite you to acknowledge that **embracing healthy choices** to improve our quality of life, health span and possibly, lifespan is **our responsibility!** Barring accidents or rare conditions, most humans today should be able to live well into their 80's and 90's. The contribution of genetics beyond the late 80's becomes progressively more important.

As we become older and "seasoned", remaining healthy, allows us to assist in the development of our children, grandchildren and our community with all the accumulated wisdom and perspective experience provide. We must remember that most chronic conditions such as hypertension, type II diabetes, obesity, vascular disease (including vascular dementia), hypercholesterolemia, etc, are intrinsically related to a sedentary life-style and inadequate diet over decades which lead to poor metabolic consequences we have discussed over many "Medical Bits".

Surprisingly, there are some physicians and healthcare systems that claim to be able to increase your "longevity" by 5-10 years.

You know that increasing your longevity depends on YOU and your healthy choices over your lifetime. Do not believe those simple pitches to grab your wallet!

For those of you who want to read one paragraph and move on to the long daily reading list and other pleasurable endeavors, the quick answer to your Longevity question is what you already know:

There is no magic pill! Increasing longevity takes hard work!

1- Eat the right way and embrace a Mediterranean diet.
2- Avoid concentrated sweets.
3- Accept intermittent fasting as much as you can tolerate, trying to approximate 14 hours, without much caloric intake (breakfasting with a few almonds or nuts) and getting most of your nutrition at dinner time gets you close to the goal.
4- Exercise daily. Both, aerobic / cardiovascular and resistance exercises help.
5- Get "uncomfortable" by exercising, fasting and accepting new challenges daily.
6- Meditate.
7- Forgo that IWatch or Fitbits in your wrist, unless you are really prepared to make the necessary changes and additional data will not lead to increasing anxiety.
8- Foster meaningful relationships with family, friends and even strangers.
9- Don't waste money in testing your "biological age" (commercial tests designed to look at "epigenetics" and cumulative DNA damage).
10- Consider some supplements: Nicotinamide, NMN, metformin, resveratrol, statins. Others are under investigation: rapamycin, mifepristone, etc.

LONGEVITY

LONGEVITY, of course, refers to the capacity to live longer than the average lifespan for the species. This brings about the deep concept of time, with its Newtonian scalar vector (moving forward) and relativity spacetime coordinates. We all have a rudimentary understanding of time, as the progression of events from the past to the present and into the future and know that it is the fourth dimension of space (a bit more complicated to comprehend for our three-dimensional world perception).

Time is intertwined with the three dimensions of space, to form spacetime and an integral part of the fabric of our Universe. Einstein demonstrated that time can slow down or speed up, depending on relative velocity and gravitational fields. For physicists, time is a “measure of space”, and its preferred direction is forward (due to the increase in Entropy – or disorder / randomness). But math and quantum mechanics physicists inform us that time can behave in unexpected manners.

Over the past two decades, the “longevity” field has grown exponentially! According to some estimates, humans spend more than $50 billion annually on some forms of “anti-aging” treatments. Most, focus on “appearance” such as cosmetic surgeries, Botox, creams, dyes. None of those deal with the all-important goal of “slowing down the clock”. But that, may be starting to change, as there are now more than 700 biotechnology companies working on different aspects of this growing field and over 250,000 articles published in the last 15 years.

Why do we age differently? What can we learn from other species?

Most complex life is made of the same building blocks (carbohydrates, lipids, proteins and nucleic acids) and yet, a mayfly lives for a day, a mouse for 2 years and a similar-sized bat for 40 years. Tortoises can live for 200 years and whales and sharks can survive for several centuries. Long-living species have a slow metabolism, stable environments, excellent DNA repair mechanisms and low risk of becoming “pray.

The underlying mechanisms of aging involve general decay at the cellular level and the body’s dwindling ability to remove old and dysfunctional cells and proteins. When we are healthy, our organs function like a well-tuned orchestra and a dynamic and active homeostasis is maintained. Aging impairs rhythmic physiologic processes and adaptation, leading to diminishing physiologic reserves available to meet new biologic challenges leading to “homeostenosis”, pushing our biology to the brink of the “precipice”.

NORMAL AGING

Aging is not a homogeneous decline. Some organs in the same person age at different rates. A Danish twin study found that genetics accounted for 25% of the variation in longevity among twins and environmental factors, for more than 50%. But after age 90, genetics becomes more important. When we are healthy, our organs function like a well-tuned orchestra and a dynamic and active homeostasis is maintained. Aging impairs rhythmic physiologic processes and adaptation, leading to diminishing physiologic reserves available to meet new biologic challenges leading to “homeostenosis”, pushing our biology to the brink of the “precipice”.

Cardiovascular System

Vascular elasticity decreases and arteries become stiff. Blood pressure rises. The left ventricle thickens, leading to diastolic stiffness and limiting maximal cardiac output and exercise tolerance. There is a marked decrease in the maximum heart rate in response to exertion (220 - age) which cannot be modified by exercise. Even if the resting left ventricular ejection fraction (LVEF) does not change in healthy elderly individuals, there are smaller increases in LVEF in response to exercise. We know that older hearts have impaired early left ventricular filling, becoming more dependent on atrial systole (explains why atrial fibrillation may lead to heart failure in the elderly). All of these changes lead to a decrease in maximum O2 utilization (VO2max) and maximal work on exercise testing.

Respiratory System

Almost 1/3 of the surface area for gas exchange is lost over the lifespan and anatomic "dead" space (non-functional lung tissue) increases. There is loss of elastic tissue with decreased expiratory lung recoil which may limit the speed of lung emptying and may lead to dynamic excessive lung inflation during exercise. Diffusion capacity (lung efficiency) declines about 5% per decade leading to a mismatch between lung ventilation and blood perfusion, worsening tolerance of hypoxia particularly at high altitudes (worse in women). The chest wall also becomes stiffer with reduction in chest wall compliance by 1/3 by age 75. The Functional vital capacity (FVC) decreases by ~ 220 ml/decade. The Forced Expiratory Volume in 1 s (FEV1) decreases by ~ 250 ml/decade. The Residual Volume (air left in the lung at the end of exhalation) rises by 10% per decade. Cough is less vigorous, muco-ciliary clearance is slower and less effective and peak aerobic capacity declines by 6% per decade in the 30's, but it can drop by almost 20% per decade beyond the 70's.

Renal System

Kidney mass declines by 25-30% between 30 and 80, but it becomes steeper after age 50, with loss of nephrons (functional unit) and decline in filtration rate by 7.5-10 ml/min per decade, although there is significant variability. The older kidney is more sensitive to toxic agents, with decreased ability to acidify and concentrate the urine and releases more aldosterone, leading to hypertension. Also, the production of klotho decreases (important protein with aging implications).

Organ System	Aging Changes
Cardiovascular System	Decreased cardiac output, increased blood pressure, arterial stiffness, and hypertrophy of the heart.
Respiratory System	Impaired gas exchange, decreased vital capacity, and slower expiratory flow rates.
Musculoskeletal System	Decreased muscle (sarcopenia), bone density (osteoporosis), and joint stiffness.
Nervous System	Slower processing speed, potential memory decline, and reduced neuroplasticity; brain volume may decrease in some areas.
Digestive System	Decreased motility, gastric acid secretion, and reduced nutrient absorption.
Renal System	Decreased renal mass and glomerular filtration rate; kidneys filter blood less efficiently.
Endocrine System	Decline in hormone production (e.g., insulin, thyroid hormones) and altered metabolic responses.

Gastrointestinal System

The oral mucosa thins with age. Gums recede. Salivary gland production declines and the propulsion of the food bolus to the pharynx is altered, along with the strength and coordination of the tongue leading to less effective mastication, decreased food clearance and increased risk of aspiration. Sleep apnea becomes more common.

Esophageal propulsion of food is also slower and the sensation of distension and tissue damage becomes impaired. The stomach is frequently the target of chronic gastritis and up to 50% of older people may be infected with Helicobacter Pilori. The endocrine stomach function may also suffer.

The small intestine suffers villus atrophy with the consequent loss of surface area with the loss of micronutrients and up to 15% of senior community residents have bacterial overgrowth, with impact on absorption.

The large intestine loses colonic propulsive motility and ½ of those older than 65 suffer from constipation. The loss of sensory neurons in the bowel decreases responsiveness and also lower pain intensity. Diverticula are present in over 65% in the US. The risk of colon cancer rises with aging. The barrier function of the colon may become compromised with increased permeability to toxins and contributing to a proinflammatory state or “inflammaging”.

The liver mass decreases by 20-40% with aging and blood flow declines by 50% by the 10th decade of life.

Genito-urinary System

Aging leads to an increase in urinary incontinence, infections, erectile dysfunction and more difficult sexual performance for both sexes. Incontinence is related to declining detrusor muscle force, bladder capacity and sphincter pressure. The increased post voiding residual inside the bladder, reduced ability to withhold voiding and nocturia (nocturnal urination) are related to decreased brain dopamine rather than local bladder abnormalities.

The absence of estrogen in women results in a shortened urethra, a lower urethral closing pressure and alterations in the local flora leading to more frequent infections. We are all familiar with the age-related prostatic enlargement and the vascular, neurologic and endocrine changes that lead to more challenging sexual performance for older men. We have reviewed the consequences of Menopause and Andropause in prior “Bits”.

Musculoskeletal System

Muscle mass decreases by approximately 30-50% in adults with muscle becoming infiltrated by fat and connective tissue with greater loss from legs and fast-twitch fibers. There is a loss of innervation and the number of motor neurons declines with greater than 50% loss in grip strength and other measures of muscle force. And as you well know, older muscles are easily fatigued and recovery after use or injury is slower, due to a defect in satellite cells, inadequate nerve recovery and altered “energetics”, as older muscle has decreased ability to generate ATP (energy) through both, the glycolytic (anaerobic) and oxidative (aerobic) pathways. Testosterone may help slow down this process but long-term studies have shown that physical activity and training raises Testosterone in a sustained manner and is safer and more effective than the pharmacologic Testosterone.

Bone

We are all familiar with the bone loss affecting the elderly and the increase risk of fractures. There is progressive decline in the number and function of Osteoblasts (bone forming cells) but Osteoclasts (bone recycling cells) remain unchanged. The overall decline in bone mass has been quantified at about 0.5% annually.

Central Nervous System

Even if your name is Albert Einstein your brain volume decreases annually after age 65, with the greatest loss in the frontal and temporal lobes with greater loss of white vs. gray matter. Blood flow also declines by 5-20%. Neuronal loss is most

prominent in the largest neurons of the cerebellum and cerebral cortex. There is also loss of synapses, but new connections and new neurons are formed throughout our lifespans. In standardized testing, for many tasks, the old brain needs to work harder, requiring more neurons and more energy for a given task, reflecting the loss of functional reserve. Processing speed declines and executive function (planning, monitoring, attention and self-preserving behavior) declines, particularly after age 70. Of course, social deprivation, environmental changes, smoking, alcohol, limited education, and lack of sleep can aggravate or exacerbate the pace of decline.

Skin

Our skin loses elasticity, and dries up. The superficial layer (epidermis) becomes thinner, the dermo-epidermal junction (interface between superficial and deeper layers) flattens and results in increased fragility unable to tolerate “shear stress” and resulting in bleeding into the space between the dermis and the epidermis (those bluish – reddish spots that appear over your arms and legs after minimal trauma). There is a decreased vascular supply and delayed wound healing with dermal collagen declining by up to 75%. Sensory perception decreases and the atrophy of subdermal fat leads to the wrinkles and sagging we all recognize.

Eye

The eyelids become more relaxed. Lacrimal tear production declines. The conjunctiva and lens yellow. This in part due to UV-light which accelerates oxidation of the lens protein and leads to “cataracts” with the consequent decreased transmission of blue light. The iris becomes more rigid and less response to light changes. Production of aqueous humor and vitreous humor declines. The retina becomes thinner due to the loss of neurons and retinal vessels and there is progressive loss of photoreceptors. As a result, the older eye faces many challenges and one of them is loss of contrast sensitivity (discrimination between object and background) and important when designing dwellings and environments for the elderly.

Hearing

Cerumen becomes drier leading to higher risk of wax impaction. The inner ear is invariably affected to various degrees with loss of hair cells in the transducer (Organ of Corti, responsible for converting the mechanical impulses into electrical signals that travel to the auditory brain centers). Cochlear neurons are lost, leading to hearing loss, especially at higher frequencies. Thus, repeating a sentence in a louder voice is not as effective as rephrasing it with different words.

Immune System

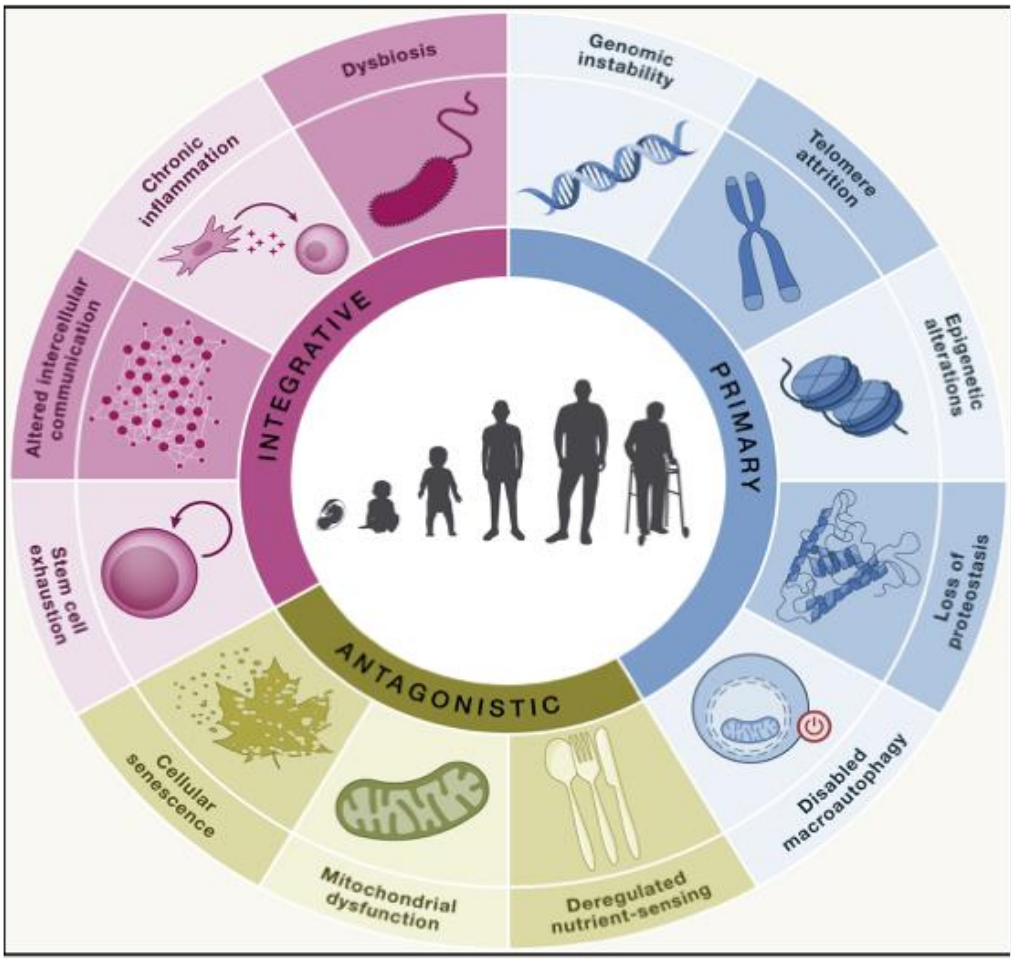
We have discussed the changes of immune-senescence in multiple other “Bits”, addressing the decline in immune function responsible for the increased susceptibility to infectious diseases, malignancy and autoimmune disorders.

What are the most important mechanisms leading to aging?

This is a subject of intense research and likely to change substantially over the next few years but not enough to abandon our certain date with Hades.

There are four major metabolic pathways associated with aging with can be possibly modified with existing molecules.

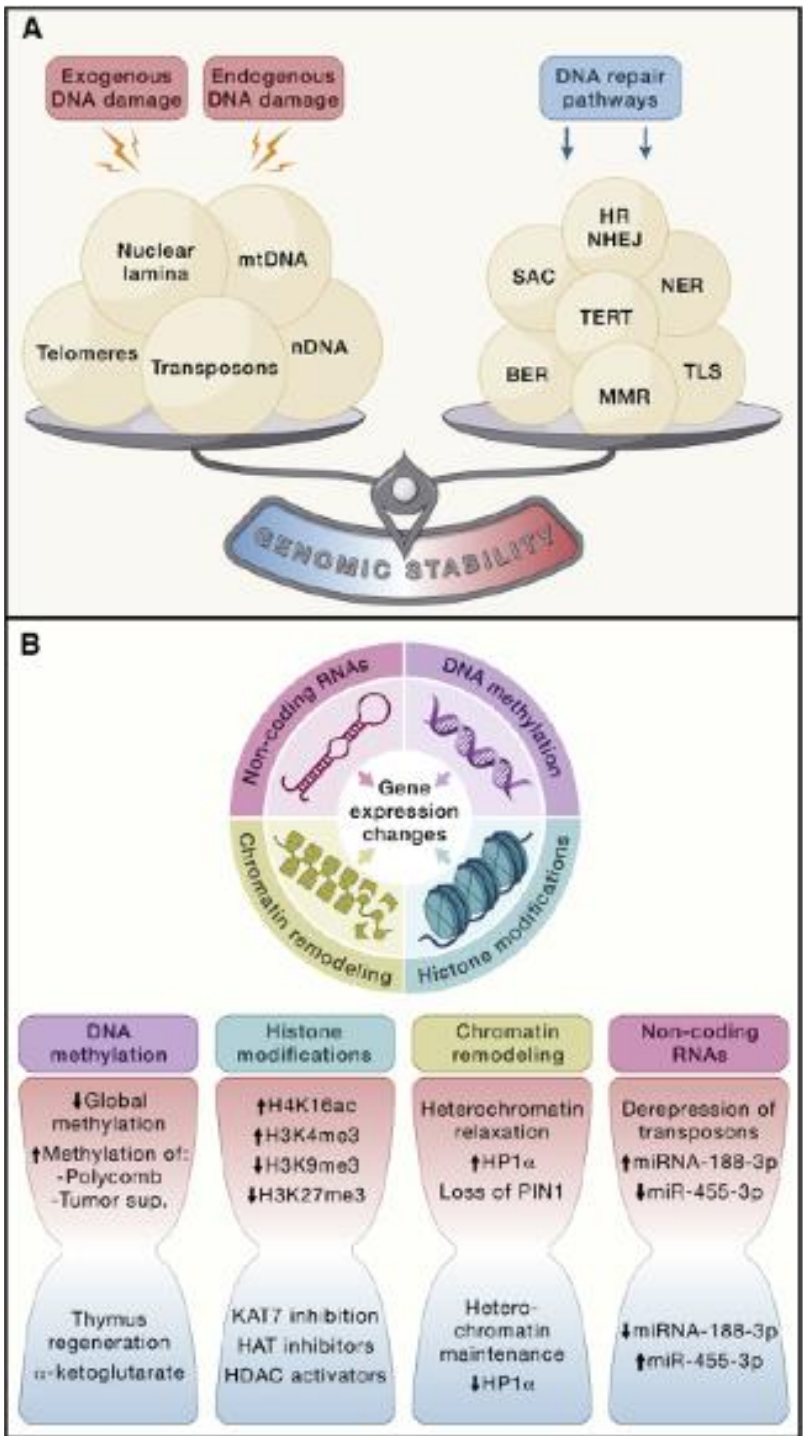
1- Insulin / IGF signaling – GLP-1 agonists such as semaglutide. “? microdosing”
2- Target of Rapamycin (mTOR). – Rapamycin derivatives.
3- Protein Kinase A (PKA) pathway. – Metformin and statins.
4- Protein deacetylase – Sirtuins pathway.



1- Damage to genetic material or “genomic instability”, due to DNA damage by UV radiation and reactive O2 species produced by our energy organelles called mitochondria. Our DNA is damaged thousands of times daily and most is repaired immediately, but some repairs are inadequate and these DNA imperfections accumulate over time leading to an increased risk of cancers, reduced cell function and cell senescence with loss of organ function as we age.

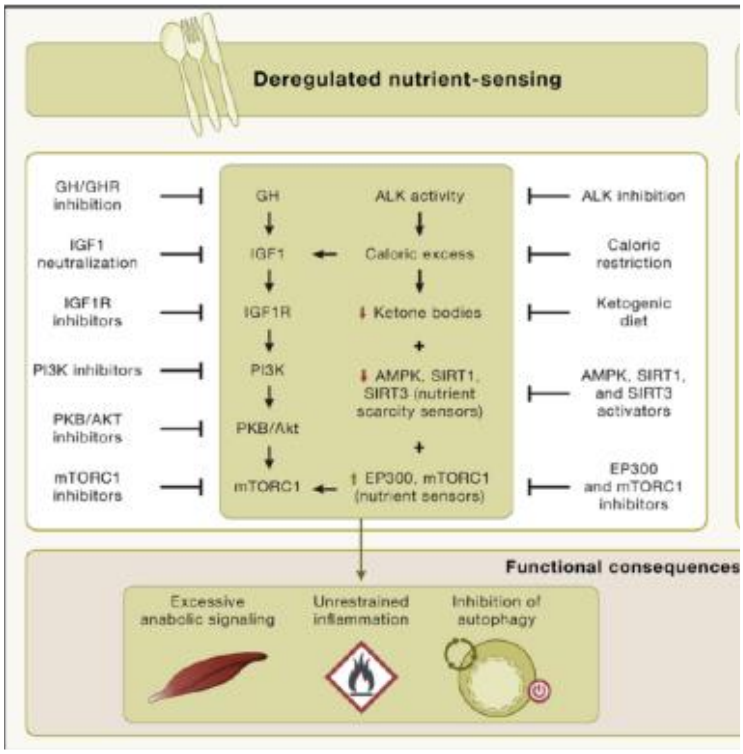
2- Telomere degradation. Telomeres are the shoelaces that keep our chromosomes intact. Every time a cell divides, telomeres shorten, eventually pushing the cells into a resting phase and halting division and replication, limiting those cells lifespan. An enzyme named telomerase can prevent shortening and restore telomere length, but the only cells expressing this enzyme are our stem cells and of course, cancer cells are characterized by high telomerase activity and “immortality”.

3- Epigenetic changes. Our genome encodes information through more than 3 billion nucleotide base pairs and chemical modifications / histone proteins that package our DNA. The accumulated chemical modifications are known as epigenome, which is dynamic and changes in response to diet, drugs, stress and aging. One of these forms of adaptation is DNA methylation and some patterns can predict a person's biological age ('epigenetic clock') and serve as a biomarker but also a potential target to modify lifespan.



4- Impaired "proteostasis". Proteins are the most important building blocks in our cells, and mediate most chemical reactions and proper cell function. Cellular systems regulate protein synthesis, folding and degradation. Damaged proteins are recycled by the proteasome or through a process of autophagy which become ineffective as we age, leading to accumulation of misfolded proteins (characteristic feature of neurodegenerative diseases such as Alzheimer's, Parkinson's, Multiple System atrophy and others. Activation of proteasome or autophagy can extend lifespan in animal models

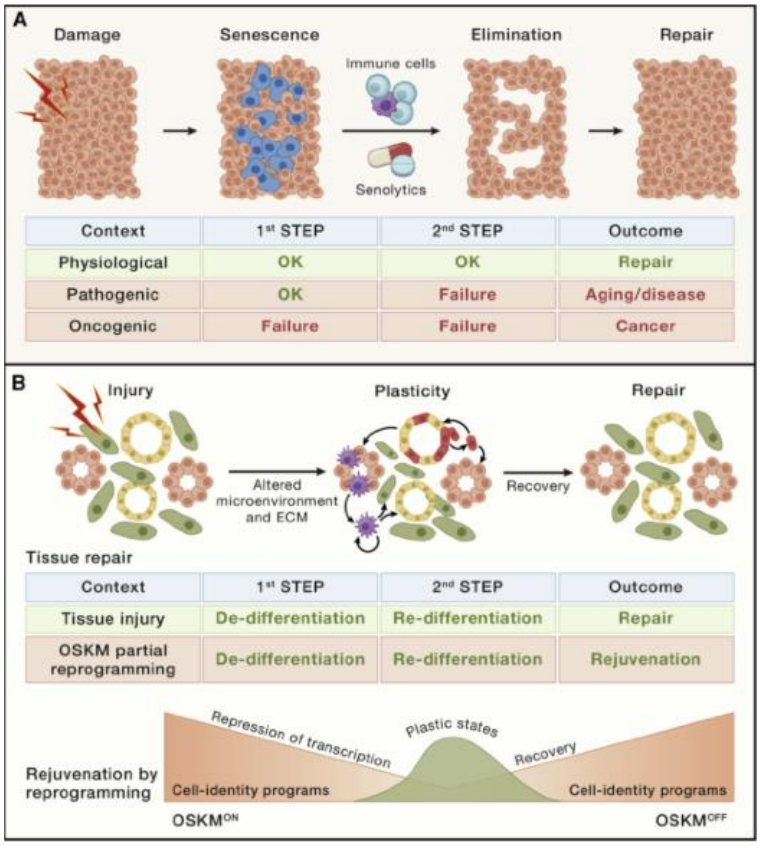
5- Impaired nutrient perception. Reduced food intake without malnutrition – Dietary Restriction – extends lifespan in multiple species. Our cells regulate growth and metabolism to the perceived availability of nutrients. Insulin and mTOR (mechanistic target of rapamycin) are important signaling systems. The latter, is preserved across multiple species and classes of organisms, and its job is to balance the need for growth and reproduction with the available nutrients. When



food is available, mTOR is activated and the cell/organism goes into growth mode, producing new proteins and replicating. When nutrients dwindle, mTOR is suppressed and cells go into “recycling” mode, triggering autophagy, breaking down cellular components with conservation of energy. There are two separate complexes: mTOR complex 1 and mTOR complex 2. The longevity-related benefits appear to be related to inhibition of complex 1.

6- Mitochondria are the cell’s energy factory or power plant, using oxygen to efficiently “burn” fuel in a process called mitochondrial aerobic respiration. They have their own DNA (mtDNA) which regulate the proteins needed for the process of fuel utilization and efficient production of energy (ATP). Aging damages mitochondrial DNA and slow down our energy power plants, allowing the accumulation of reactive oxygen species and free radicals.

7- Cellular senescence. Stress and cumulative damage may lead the cells to enter a state of senescence. Cells stop dividing, lose original function and release inflammatory cytokines and mediators impacting surrounding cells and organic function. There are many triggers for cellular senescence, including telomeric shortening, DNA damage and mitochondrial dysfunction and now new drugs are being tested to silence these senescent cells (called senolytics) and potentially improve aging.



8- Stem cell exhaustion. The cells in our tissues lose the ability to divide once they reach their final destination and identity, but stem cells have

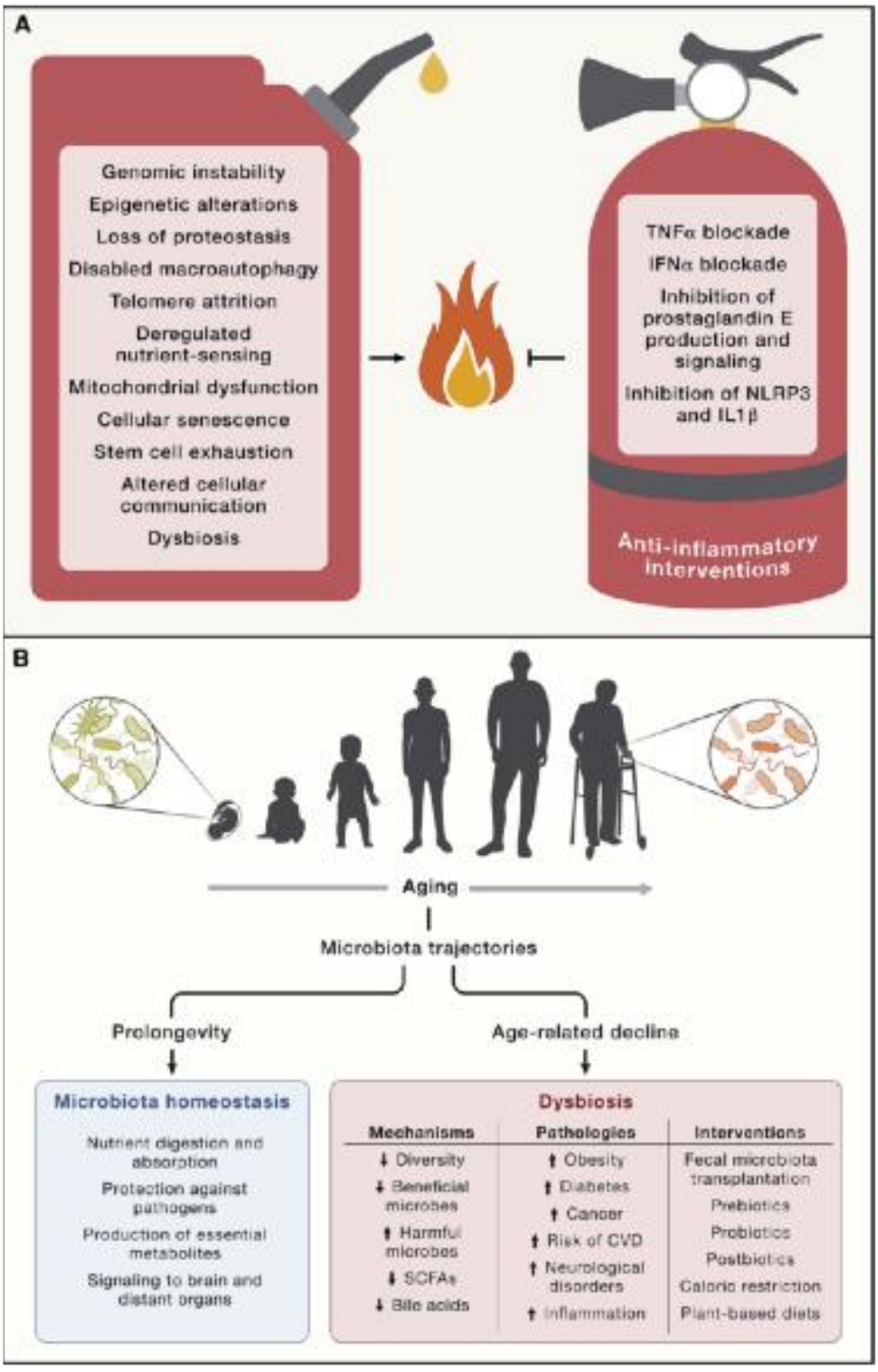
the ability to divide and differentiate into different cell types and are important to repair tissues and organs. Aging results in stem cell depletion leading to a limited ability to repair organ damage. New research indicates that old stem cells can be ‘rejuvenated” leading to improved organ function.

9- Altered intra and intercellular communication is another hallmark of aging.

10- Degraded autophagy: the body’s break down of unwanted cell components deteriorates with aging.

11- Chronic inflammation at low-level is a hallmark of aging.

12- Dysbiosis (imbalance) of intestinal flora: There is good evidence that centenarians have a healthier flora and microbiome.



PROMISING DRUGS TO EXTEND HUMAN LIFE:

Drug	Action	Effects on Longevity	Notes
Mifepristone	Increases mitophagy, enhancing mitochondrial health.	Extended lifespan in fruit flies; potential for human trials as an anti-aging treatment.	Approved for other medical uses, which may expedite clinical testing for longevity effects.
Rapamycin	mTOR inhibitor that promotes autophagy and cellular maintenance.	Increased lifespan by 10-15% in mice; effective even when administered late in life.	Considered one of the most robust compounds for longevity in mammalian studies.
Metformin	Activates AMPK, mimicking dietary restriction effects.	Associated with a 5% increase in male mouse lifespan; widely used for type 2 diabetes and deemed safe for humans.	Potentially beneficial in reducing risks of age-related diseases 24.

We will elaborate on these agents and other promising supplements / strategies on Medical Bits – Longevity Part II.

In the meantime, grab your shoes and get moving!

Doing your best to stay healthy is your most powerful strategy!

DEBUNKING MYTHS: Q & A

Should we all take medical supplements? MYTH!

As we discussed in the past, almost 60% of Americans consumes vitamins, minerals, botanicals, live microorganisms, probiotics and dietary supplements (spending about 55 billion in 2020) to prevent or treat various (mostly) imaginary ailments and “conditions” (infections of all sorts, memory loss, lack of energy, heart disease, aging, degenerative bone disease, etc.) you may want to read the Dietary Supplement Listing Act of 2022 and will realize why it’s always best to “keep it simple” and if not proven, do not use them.
The FDA reports that are more than 95,000 supplements on the market today and the vast majority have not been tested for safety or effectiveness.

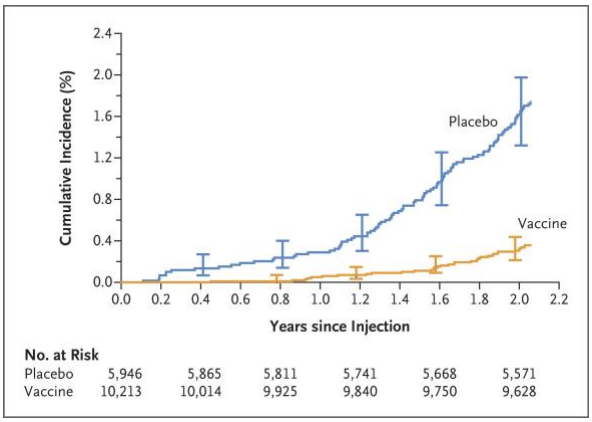
What are the exceptions where supplements may be beneficial?

1. Laboratory testing has demonstrated a deficiency of specific vitamins or minerals (Only to be tested in particular situations).
2. Vegan individuals are frequently deficient in Vitamin B12, as animal sources are rich in B12. Also, patients who had a gastric or terminal ileal resection.
3. Individuals with Inflammatory Bowel Disease (UC or CD) or GI conditions with associated malabsorption syndromes may need fat-soluble vitamins (A-D-E-K).
4. All Cystic Fibrosis patients.
5. Most patients with prior Bariatric Surgery.
6. Pregnant women need to add Folic Acid and Prenatal Vitamins with iron.
7. Multivitamins might slow cognitive decline, but more research necessary.
8. AREDS supplements (Vitamins C, E, Copper, Lutein and Zeaxanthin) may slow vision loss in those with age-related macular degeneration.

There is no MAGIC PILL and NO SUBSTITUTE FOR EXERCISE and a HEALTHY PROTEINACEOUS DIET!

Word of caution: As you have read, the Caribbean, Central and northern South America have become endemic for **Dengue**. Beware of Mosquitoes and use daily repellent and long-sleeves!

There is no effective vaccine against Dengue but this is a new promising vaccine hopefully available soon!



If you have 10 minutes, enjoy this time-lapse of the Entire Universe.

If you have 6 more minutes, the massive expanse of our Universe and the magnificent insignificance of humanity will delight you.

You will not be able to watch these two videos without smiling.

7 Minutes can start to improve your fitness right now with the Scientific 7- Minute Workout. Get the app

11 more minutes will get you in shape!

For core strength, try this 9-minute routine!

Can you pass this 10-second BALANCE TEST?
Take the 30-second Power Test

And splurge on the 30-minute power-building workout!
Embrace fitness! Exercise is candy to our muscles and they need daily intermittent activity to remain metabolically healthy!
Remember that every woman benefits from Pelvic Floor exercises and should be part of their routine.
START EXPLORING MINDFULNESS!
It lowers your BP, stress and raises pain threshold and well-being.
RESOURCES ON THE WEB.

The only certainty in life, is death and the only fountains of youth proven by science and experience are love, exercise, laughter, humor and a positive attitude!

Wishing you a Happy, Healthy and Prosperous 2025!

OFFICE UPDATES

- As you know, we have opened our Premier Medicine – Concierge Internal Medicine and Consultative Pulmonary Medicine practice and moved to our temporary office at the Barlow Building, 5454 Wisconsin Ave Suite 1265. We will move to our final move when our suite's buildout is completed by April 2025. All of our staff are familiar to you and always willing to help!
- Ashley Alvarez is our secretary and front desk supervisor, ready to assist with your scheduling needs at aalvarez@premier-medicine.com or by calling our office at 301-637-5555.
- Brenda Perez is our office manager who can troubleshoot any insurance problems or office matters at bperez@premier-medicine.com
- Emily Swearingen (Emily.swearingen@premier-medicine.com) is one of our Medical Assistants always willing to help and becoming our Respiratory Technician as she works towards Medical School acceptance in 2026.
- Olivia Dragovits (odragovits@premier-medicine.com) is one of our Medical Assistants and in charge of SMD / Signature MD matters, always ready to help as she works towards her Medical School acceptance in 2026.
- We have hired a wonderful Nurse Practitioner – Irene Burgos, NP and will join us on Feb 1st, 2025.
- Some of our former assistants whom you know, continue to make progress towards their medical degrees. Patty Zhao graduated from UVa in 2024. Emily Ferguson is a 4th year student at Jefferson University in PA. Simran Singh is now in her third-year Med School at University of Buffalo. Samantha Morales is at the University of South Carolina School of Medicine and Andrew Fookes at Georgetown University and both advancing to their second year.

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