Quest for Immortality & Vitality

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Clinical Professor of Medicine
University of California, San Diego

"I don't want to achieve immortality through my work. I want to achieve it through not dying." ~ Woody Allen

The timeline from the first flight to supersonic transport and the first rocket to a manned mission to the moon have been breathtakingly brief. The first theory that a chemical means of transmission of genetic information, to the identification of DNA, took a few years. The progress since then leading to new fields of genomics, epigenetics, gene sequencing, gene correction, and transfer has been nothing short of revolutionary. The life span of various rodents is remarkably varied, and even more varied are the lifespans of different animals. Some life forms have been identified that have lifespans measured in the thousands of years, others appear to be immortal.

The Nobel Prize in Medicine or Physiology was awarded to Dr. Sydney Brenner for his work on the genetics of the roundworm, which has parallels to the genomics of man. Modifying one single gene led to a near ten-fold increase in its lifespan, the human equivalent of reaching an age one thousand years. The single cell at fertilization, through replication and cell division, becomes over 37 trillion specialized cells in the adult. Each cell carries a duplicate of the DNA of its parent cells unless a mutation occurs. The power of exponential or logarithmic growth is often vastly underestimated. Human life expectancy has increased, predominantly through reductions in infant mortality.

Free radicals, oxidation, and inflammation and are the biological equivalent of rust and aging. Genes are not destiny; epigenetic influences from the environment modify genes as well as turning them on and off. Telomeres, the ends of the chromosomes that act as the equivalent of shoelace caplets, prevent the unraveling of DNA and cell death. The enzyme telomerase prevents the shortening of telomeres and enhances cell longevity. Cancer cells use telomerase to maintain cancer cell viability and propagation, making some cancer cell lines virtually immortal. Genetic mutations that trigger accelerated aging, such as progeria, are providing important insight into the mechanisms of aging that offers potential therapy to control the aging process. One of the control genes of aging found in the roundworm is also present in mouse and man. A metabolite of a microbe found in the soil of Easter Island influences this gene and leads to extended lifespan in the roundworm, and evidence of age reversal in mice. This compound is FDA

approved for treating post organ transplant patients to prevent rejection, and human trials to assess its effect on aging are ongoing. Laboratory advances in roundworms and mice are providing important insights, but applications in humans require extensive study, even if the sane genes are shared between species. The advent of new technology, such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has brought gene transfer and correction of genetic mutations from the world of science fiction to present day reality.

On occasion, the result of a new scientific advance meets or exceeds the initial hype. Stem cells are one example where the advances have rapidly moved from the laboratory to clinical applications. Stem cell therapy has moved from the laboratory to clinical applications relatively rapidly. The first stem cell transplant took place over fifty years ago with bone marrow transplants. The condition amenable to new approaches with stem cells is expanding rapidly. Organ regeneration and replacement, as well as cloning for organ retrieval, are no longer science fiction but on the horizon. Limb and organ regeneration from stem cells and gene transfers to correct mutations or provide new properties are within technological reach. Advances in technology have made prosthetics that have similar or superior properties to the human original possible. Further advances will accelerate advances over the natural features, and even today the Olympics disallow blade runners who have a speeds advantage over normal limbs. Many of the diseases that result in death today, such as myocardial infarction and heart failure, are theoretically curable with a mechanical prosthetic heart or one regenerated from stem cells.

Nanotechnology is rapidly advancing, and an entirely new field of technology and medicine will offer remarkable diagnostic and therapeutic advances. Hormones were the original focus of aging and vitality research and continued to have an important role to play. Testosterone and growth hormone supplements are not without risks, and the science of longevity and age management is rapidly advancing beyond hormone therapy. Lifestyle, diet, stress, inflammation, and a variety of factors have been identified by studying centenarians, those who have lived a century or more, in 'blue zone' communities around the world where they are found in sizeable number. Caloric restriction extends lifespan in mice and other organisms. Some humans are adapting this approach, with the results unknown as yet. Laboratory research has identified compounds that mimic the effect of caloric restriction, so it is possible that in the future you can literally have your cake and eat it too!

Diet plays an important role in inflammation and its management. Many people believe inflammation should be referred to as inflamed-aging because of its profound effect on the aging process. Red wine and resveratrol have received a lot of publicity for anti-aging effects, but to date the results of resveratrol compounds have been disappointing. One of the lessons learned from the concept of systems biology is that individual components may require other factors to achieve results. So even though resveratrol by itself may not have proven benefits, perhaps when taken with other key components in the elixir of red wine, it is beneficial. The Mediterranean diet, as well as the red wine industry, suggests this is the correct path to take, in moderation of course.

Without a doubt, exercise appears to have the greatest anti-aging effects known to date. Perhaps one day the benefit will be available in pill form, but even then you should take the pill for a long walk each day before swallowing it! The diet we consume undoubtedly is another key to our health and longevity. It may have a direct influence by its components, or indirect via changes in epigenetics and the microbiome. Even when the diet appeared to play a direct role, such as fat content and cardiovascular risk, the truth was much more complicated. For example, phosphatidylcholine is a vital phospholipid substance found in every cell of the human body. As it was first identified in eggs it was given the name lecithin derived from the Greek word lekithos (λεκιθος, egg yolk).

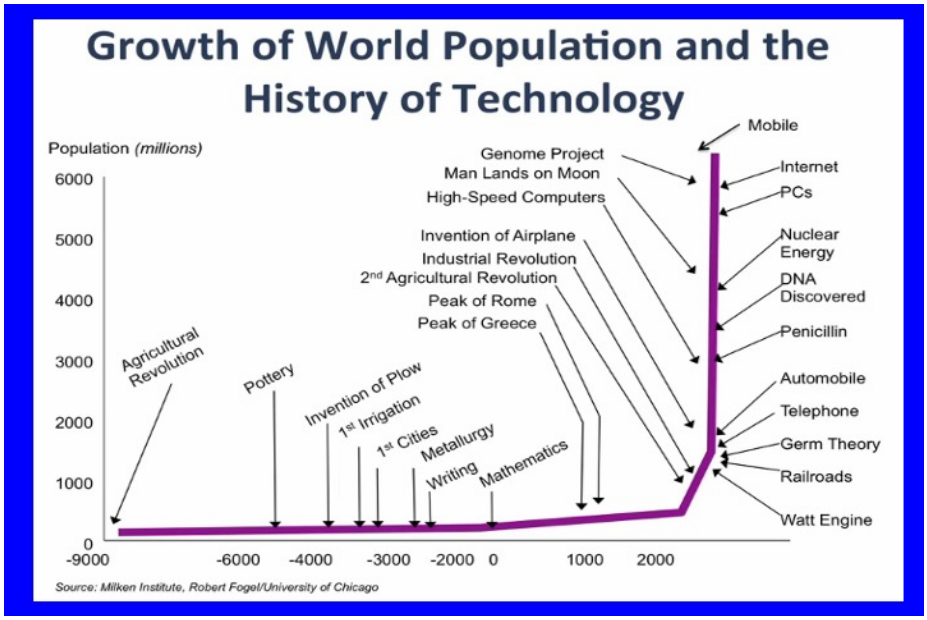
The Western diet is rich in lecithin, which the gut microbes use to create trimethylamine, which is then absorbed by the gut and converted by the liver to TMAO. Choline, betaine, and trimethylamine N-oxide (TMAO) are metabolites of lecithin and are associated with cardiovascular risk in humans. TMAO has

been associated with accelerated atherosclerosis, enhanced playlet hyper-reactivity, and thrombosis risk. Vegetarian, vegan, and Mediterranean diets (dairy, eggs, legumes, vegetables, seafood) are associated with lower TMAO levels. Gut microbial suppression with antibiotics reduces plasma levels of TMAO. Who would have imagined that the food was influenced by the microbiome, and then metabolized by the liver, and then could affect the cardiovascular system?

The human microbiome and its genes have a profound influence on human health. We are constantly exposed to new organisms, and the microbiome is always adapting. The use of probiotics, antibiotics, prebiotics, dietary supplements, nutraceuticals, prescription and over the counter drugs can affect the microbiome in so many ways that the consequences cannot be predicted with certainty. What can be predicted is that they will be heavily marketed and promoted because there is a huge profit to be made, and safety and efficacy are secondary afterthoughts. Sometimes the wisdom of sages past cannot be improved upon, this is one of them. Some cancers, such as breast and colon, can be identified early when highly curable. Surveillance for those at higher risk is suggested. Further advances in genomics may identify populations at risk, and blood tests may replace the screening tests we use today. Colon cancer screening is suggested for those over fifty years of age, and for younger individuals who have a history or family history of colon cancer, colon polyps, inflammatory bowel disease, and specific genetic markers.

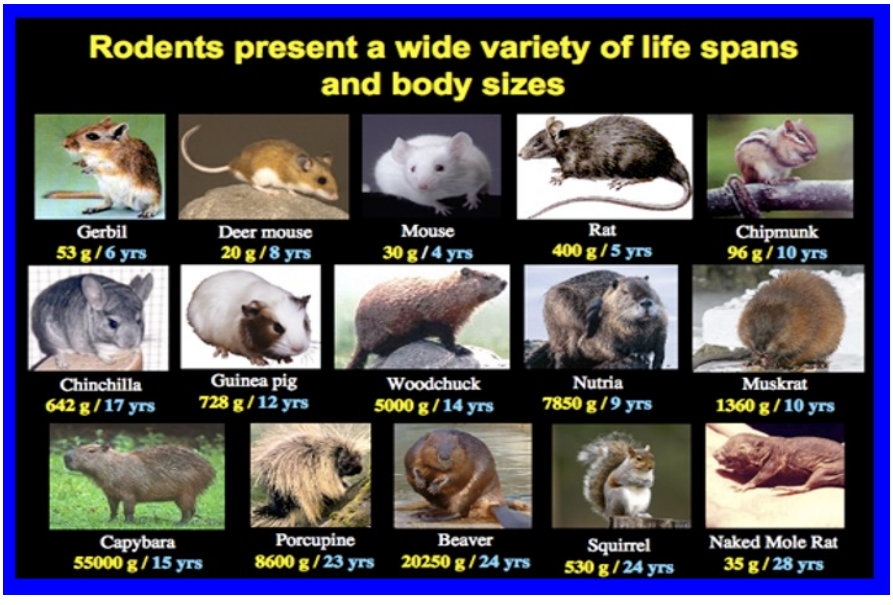
Colonoscopy has been the 'gold standard', but new options include capsule colonoscopy, a high-tech image transmitter that is swallowed and sends images for review. The latest FDA-approved test was a fecal (stool) DNA test for markers of colon cancer and polyps. Technology and approaches are changing, but getting screened may well be a lifesaver, as these cancers often do not exhibit signs or symptoms until they are no longer curable. Freezing the whole body, or just the head, for hopeful revitalization has a market and a rationale, but a whole host of obstacles make the technological feasibility of returning in the future uncertain. Personalized medicine, utilizing genomics and other technology, is the future of medicine. The 'one size fits all' approach to population-based medicine has been a disaster that the public is, for the most part, unaware of.

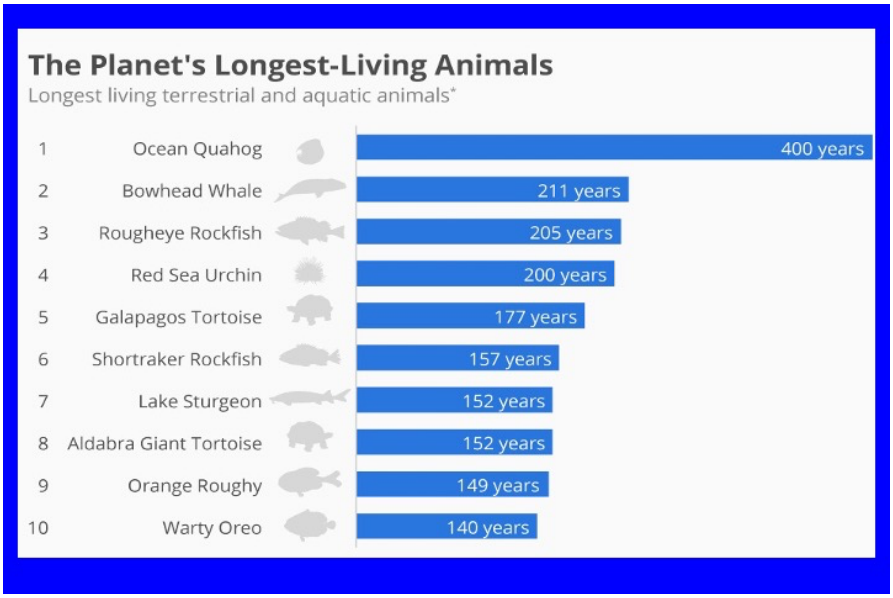
The cover of Time magazine prophesizing 2045 as the year man becomes immortal is based on the concept of singularity, downloading your consciousness and brain onto a computer cyborg equivalent. This will probably become an option, to have a virtual life and existence, with equally complex moral and social choices. The possibility of becoming an electronic mind reminds me of a cartoon image of a janitor unplugging a complex life support technology to plug in his floor polisher.



Evidence-Based Medicine

"Over two million articles are published annually in the biomedical literature in over 20 000 journals"

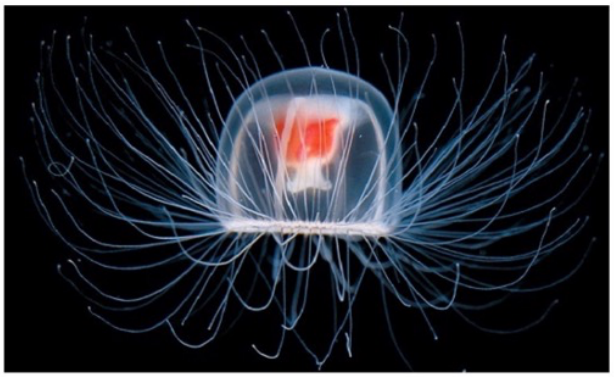



The Planet's Longest-Living Animals
Longest living terrestrial and aquatic animals*
1 Ocean Quahog 400 years
2 Bowhead Whale 211 years
3 Rougheye Rockfish 205 years
4 Red Sea Urchin 200 years
5 Galapagos Tortoise 177 years
6 Shortraker Rockfish 157 years
7 Lake Sturgeon 152 years
8 Aldabra Giant Tortoise 152 years
9 Orange Roughy 149 years
10 Warty Oreo 140 years

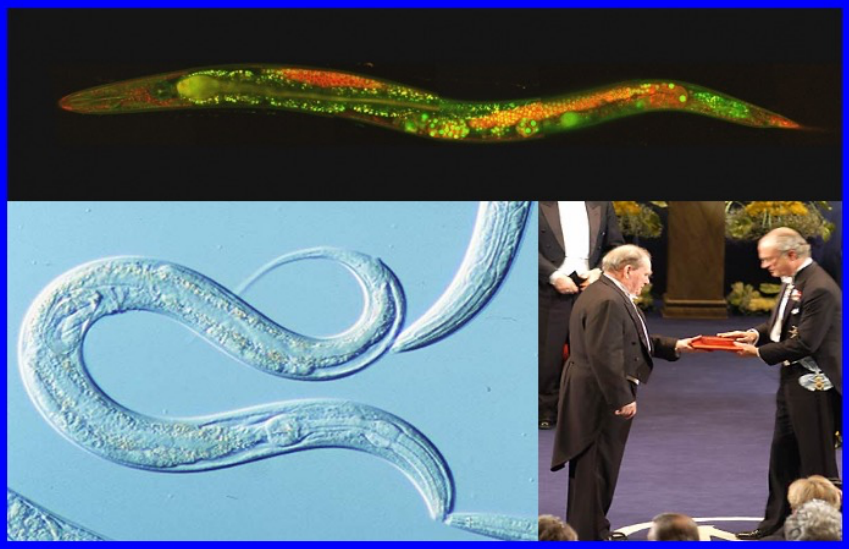

2. King's Lomatia
Age: at least 43,600 yeas old (possibly up to 135,000 years)
Location: Tasmania
Species: Lomatia tasmanica


Jellyfish and lobsters are considered biologically immortal. They don't age and will never die unless they are killed.
Lobsters do not weaken, slow down, or lose fertility due to aging. This may be due to an enzyme called telomerase that repairs DNA sequences.

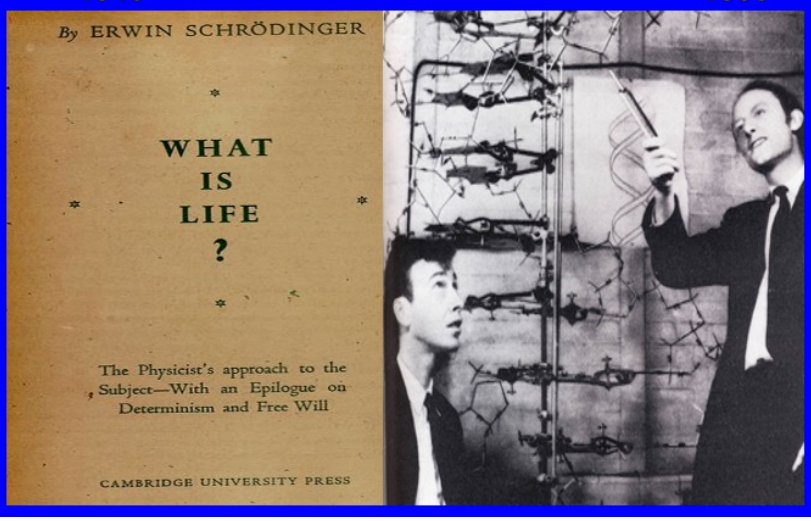
1. TURRITOPSIS NUTRICULA JELLYFISH

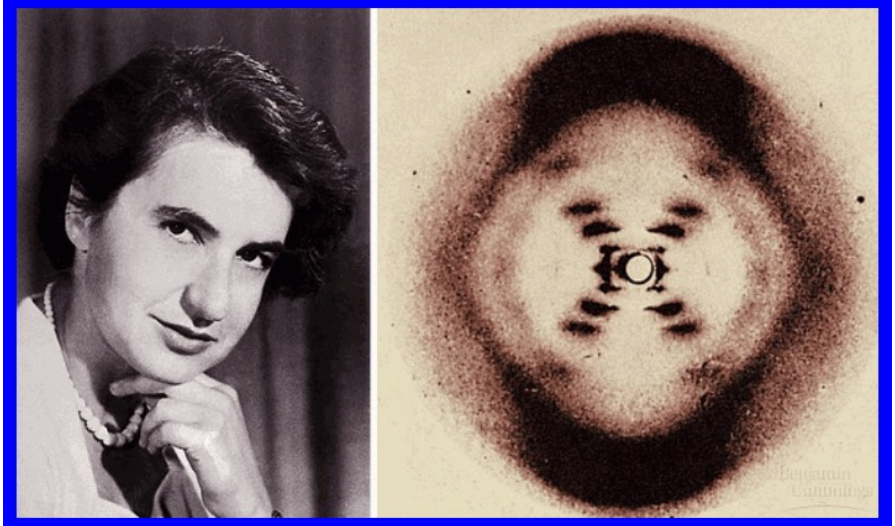


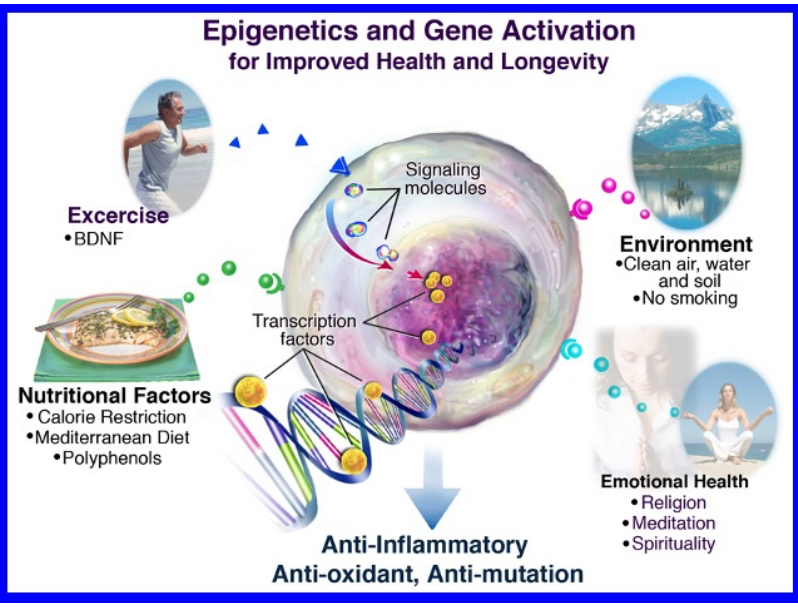
Amazingly, this species of jellyfish has been known to be immortal because it has the capability of returning from its mature stage to the immature polyp stage and this process continues on and on. This makes the Turritopsis Nutricola Jellyfish the undisputed leader on this list.

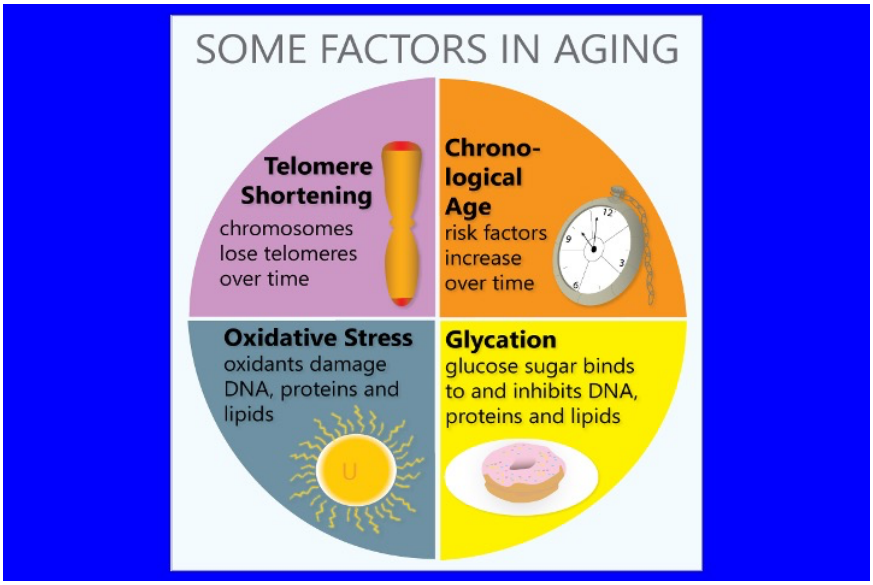


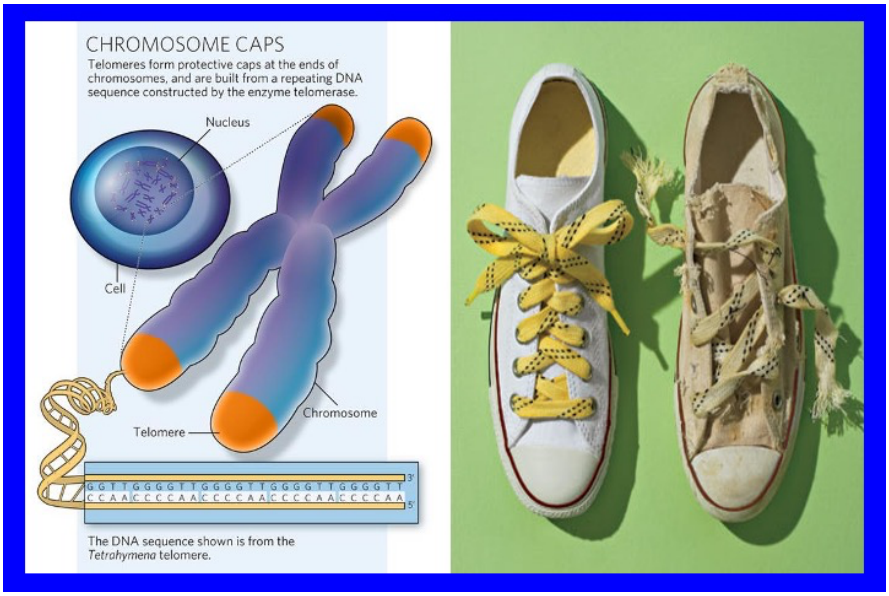
1946 1953

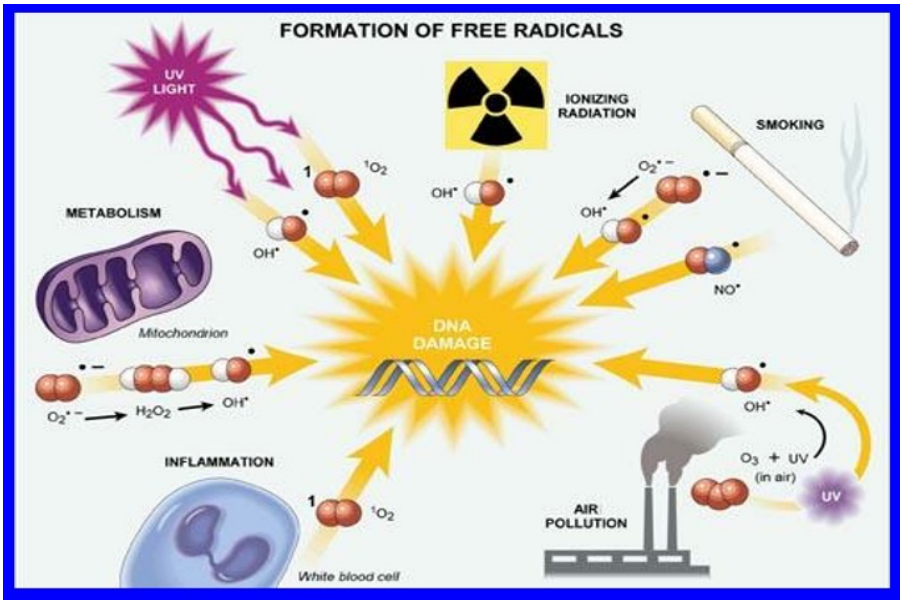

By ERWIN SCHRÖDINGER
WHAT
IS
LIFE
?
The Physicist's approach to the Subject—With an Epilogue on Determinism and Free Will
CAMBRIDGE UNIVERSITY PRESS

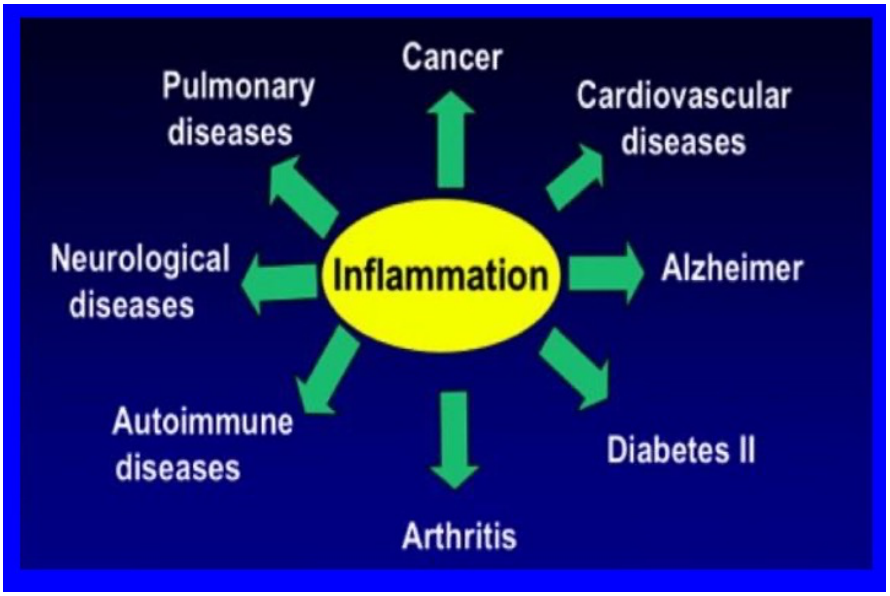



Epigenetics and Gene Activation
for Improved Health and Longevity
Excercise
•BDNF
Signaling molecules
Environment
•Clean air, water and soil
•No smoking
Transcription factors
Nutritional Factors
• Calorie Restriction
•Mediterranean Diet
•Polyphenols
Emotional Health
• Religion
• Meditation
• Spirituality
Anti-Inflammatory
Anti-oxidant, Anti-mutation

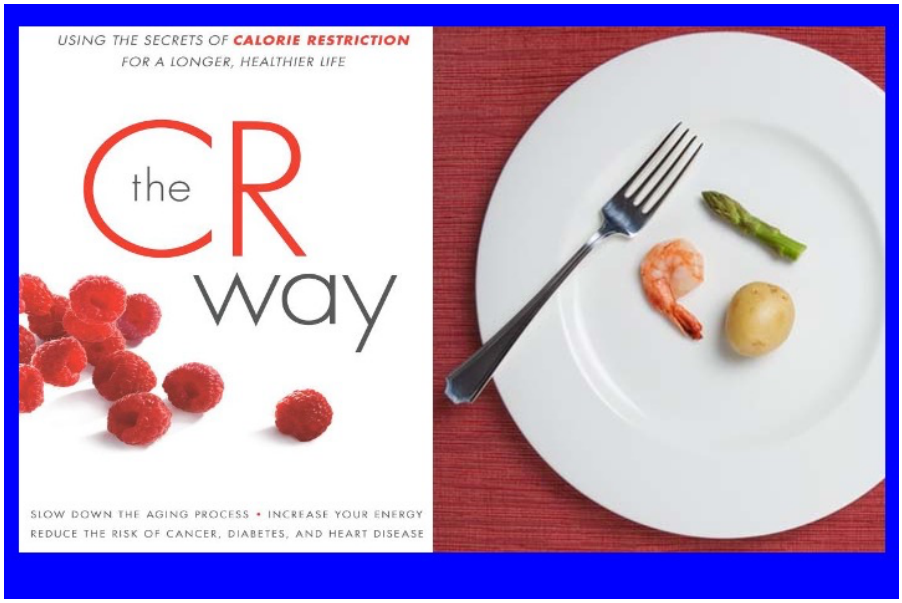

SOME FACTORS IN AGING
Telomere Shortening
chromosomes lose telomeres over time
Chrono-logical Age
risk factors increase over time
Oxidative Stress
oxidants damage DNA, proteins and lipids
Glycation
glucose sugar binds to and inhibits DNA, proteins and lipids


CHROMOSOME CAPS
Telomeres form protective caps at the ends of chromosomes, and are built from a repeating DNA sequence constructed by the enzyme telomerase.
Nucleus
Cell
Chromosome
Telomere
The DNA sequence shown is from the Tetrahymena telomere.

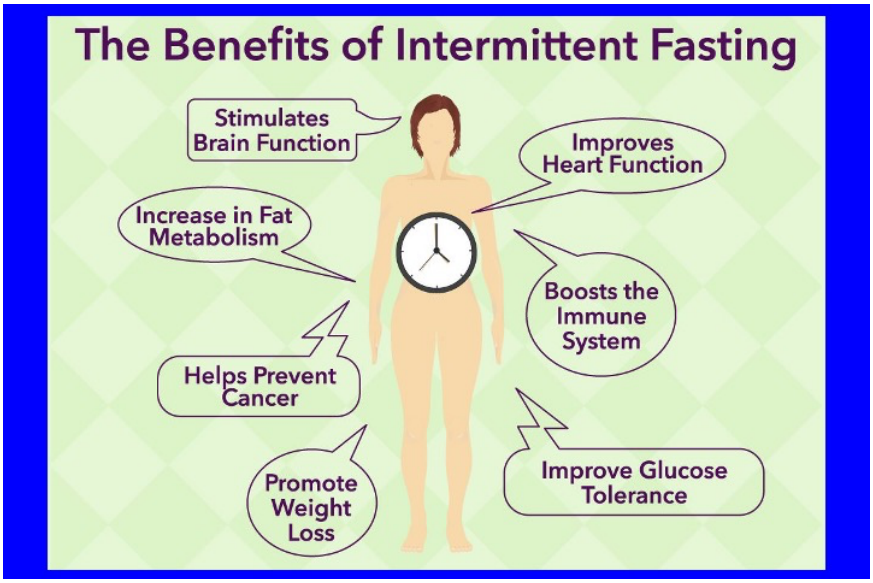

FORMATION OF FREE RADICALS
UV LIGHT
IONIZING RADIATION
SMOKING
METABOLISM
Mitochondrion
DNA DAMAGE
INFLAMMATION
White blood cell
AIR POLLUTION
(in air)
UV


Cancer
Pulmonary diseases
Cardiovascular diseases
Neurological diseases
Inflammation
Alzheimer
Autoimmune diseases
Diabetes II
Arthritis

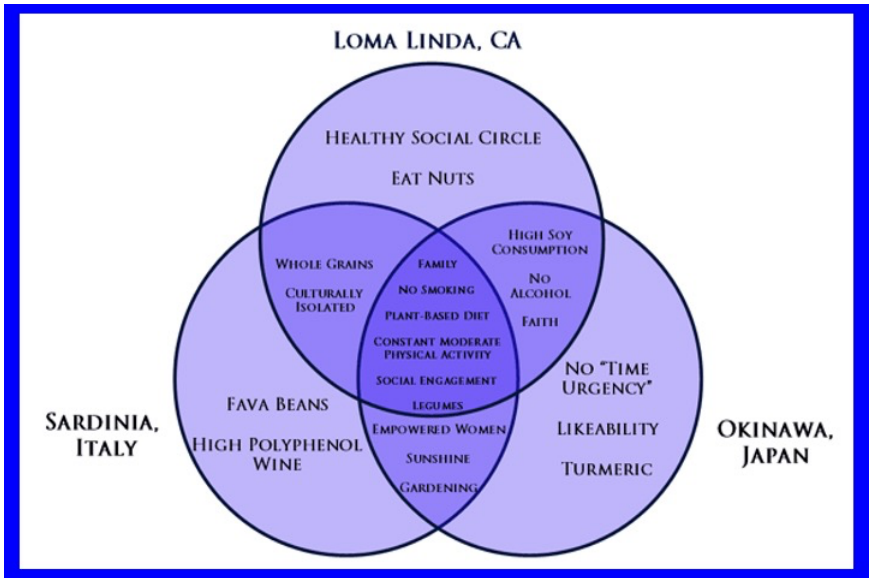

Dark Chocolate
TOP ANTIOXIDANT FOODS
ORAC* UNITS PER 100 GRAMS
Dark Chocolate 13,120
Milk Chocolate 6,740
Prunes 5,770
Raisins 2,830
Blueberries 2,400
Blackberries 2,036
Kale 1,770
Strawberries 1,540
Spinach 1,260
Raspberries 1,220
Brussels sprouts 980
Plums 949
Alfalfa sprouts 930
Broccoli florets 890
Oranges 750
Grapes, red 739
Red bell pepper 710
Cherries 670
Onion 450
Corn 400
Eggplant 390
* ORAC (Oxygen Radical Absorbance Capacity) is a measure of the ability of foods to subdue harmful oxygen free radicals that can damage our bodies.
Source: Data from U.S. Department of Agriculture and the Journal of the American Chemical Society.

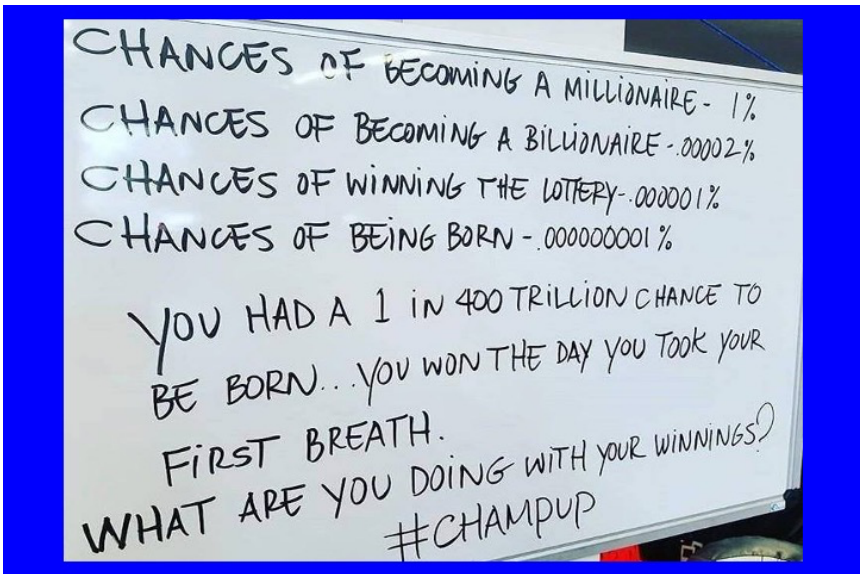

USING THE SECRETS OF CALORIE RESTRICTION
FOR A LONGER, HEALTHIER LIFE
the CR way
SLOW DOWN THE AGING PROCESS • INCREASE YOUR ENERGY
REDUCE THE RISK OF CANCER, DIABETES, AND HEART DISEASE

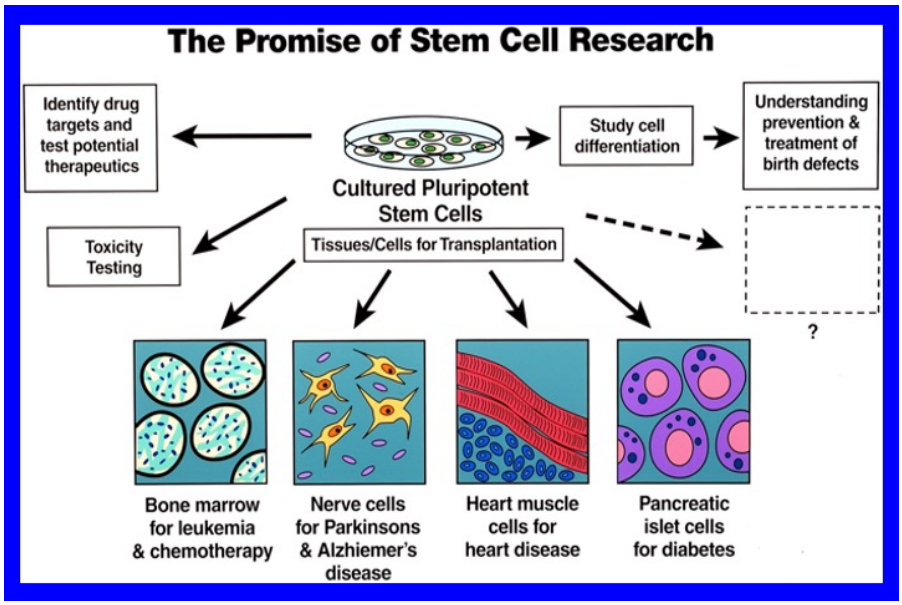

5 Types of Fasting
Simple Fast: 12 hours
Cycle Fast: 16 hours - 3x weekly
Strong Fast: 16-18 hours daily
Warrior Fast: 19-21 hours daily
1 Day Fast: Full 24 hour fast each week

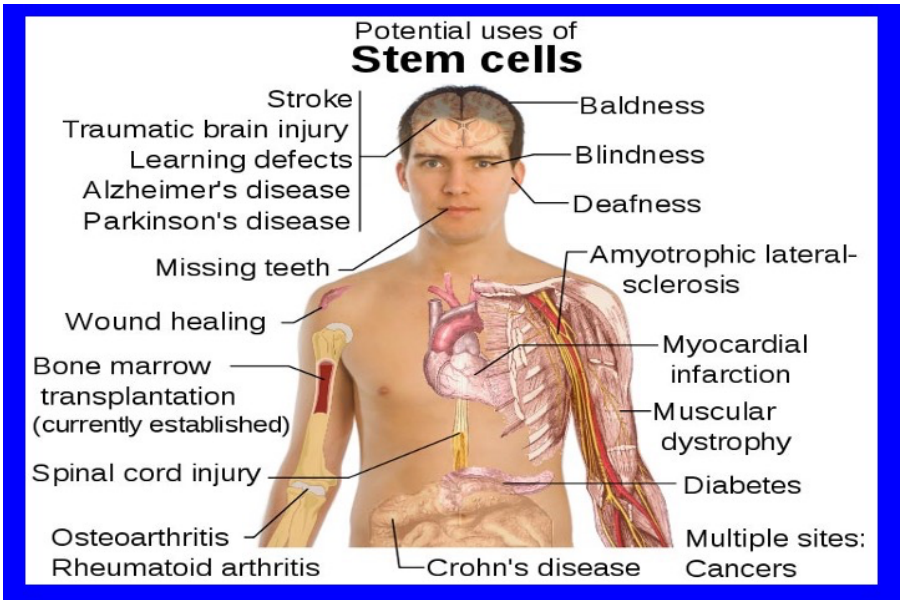

The Benefits of Intermittent Fasting
Stimulates Brain Function
Improves Heart Function
Increase in Fat Metabolism
Boosts the Immune System
Helps Prevent Cancer
Promote Weight Loss
Improve Glucose Tolerance


LOMA LINDA
CALIFORNIA
SARDINIA
ITALY
ICARIA
GREECE
OKINAWA
JAPAN
NICOYA
COSTA RICA
BLUE ZONES
LONGEVITY HOTSPOTS
BLUE ZONE LIFE LESSONS
MOVE NATURALLY
RIGHT TRIBE
RIGHT OUTLOOK
EAT WISELY


LOMA LINDA, CA
HEALTHY SOCIAL CIRCLE
EAT NUTS
WHOLE GRAINS
CULTURALLY ISOLATED
FAMILY
NO SMOKING
PLANT-BASED DIET
CONSTANT MODERATE PHYSICAL ACTIVITY
SOCIAL ENGAGEMENT
LEGUMES
EMPOWERED WOMEN
SUNSHINE
GARDENING
HIGH SOY CONSUMPTION
NO ALCOHOL
FAITH
NO "TIME URGENCY"
LIKEABILITY
TURMERIC
SARDINIA, ITALY
FAVA BEANS
HIGH POLYPHENOL WINE
OKINAWA, JAPAN

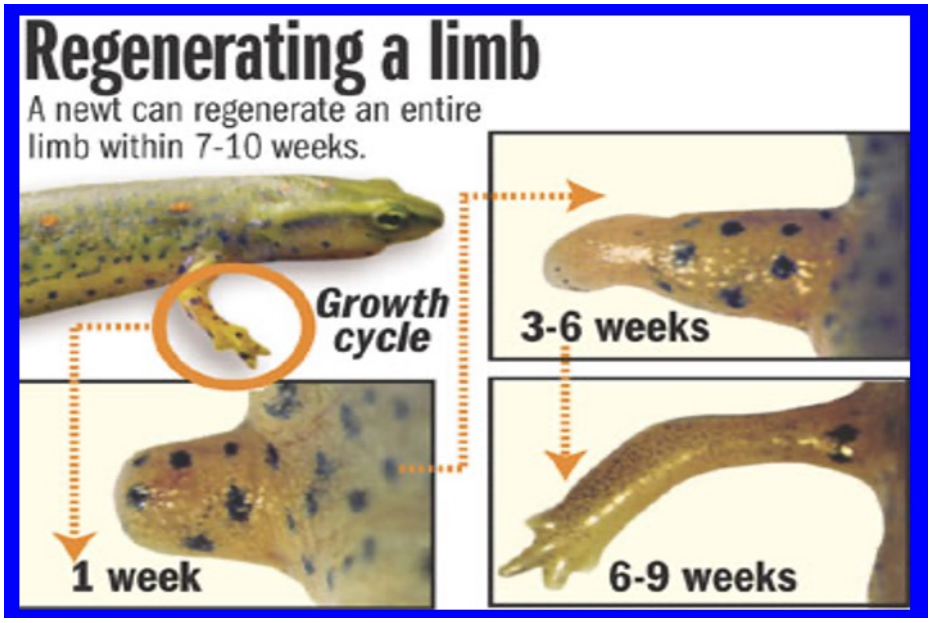

CHANCES OF BECOMING A MILLIONAIRE - 1%
CHANCES OF BECOMING A BILLIONAIRE - .00002%
CHANCES OF WINNING THE LOTTERY - .000001%
CHANCES OF BEING BORN - .000000001%
YOU HAD A 1 IN 400 TRILLION CHANCE TO BE BORN... YOU WON THE DAY YOU TOOK YOUR FIRST BREATH.
WHAT ARE YOU DOING WITH YOUR WINNINGS?
#CHAMPUP

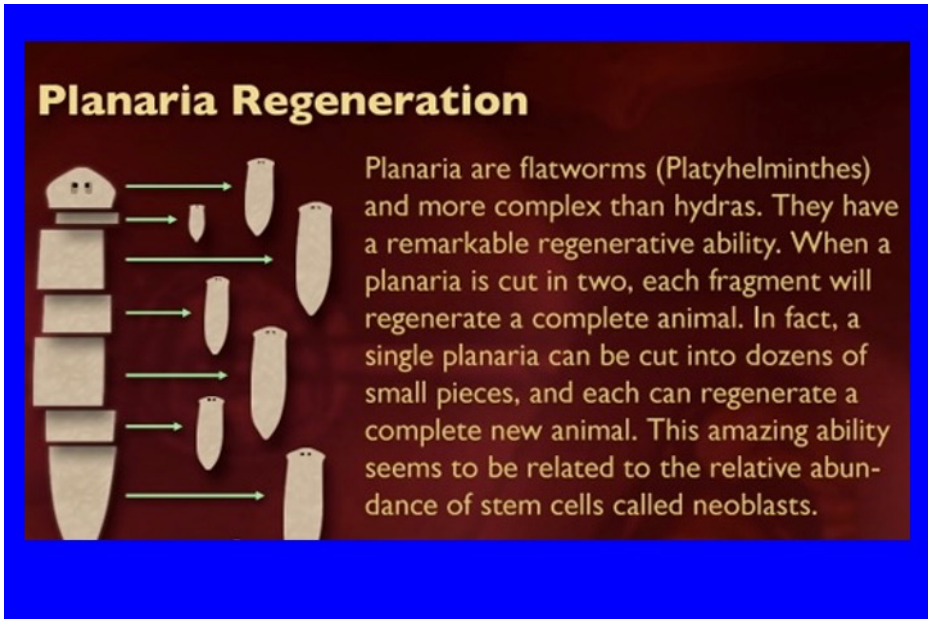

The Promise of Stem Cell Research
Identify drug targets and test potential therapeutics
Cultured Pluripotent Stem Cells
Study cell differentiation
Understanding prevention & treatment of birth defects
Toxicity Testing
Tissues/Cells for Transplantation
?
Bone marrow for leukemia & chemotherapy
Nerve cells for Parkinsons & Alzhiemer's disease
Heart muscle cells for heart disease
Pancreatic islet cells for diabetes

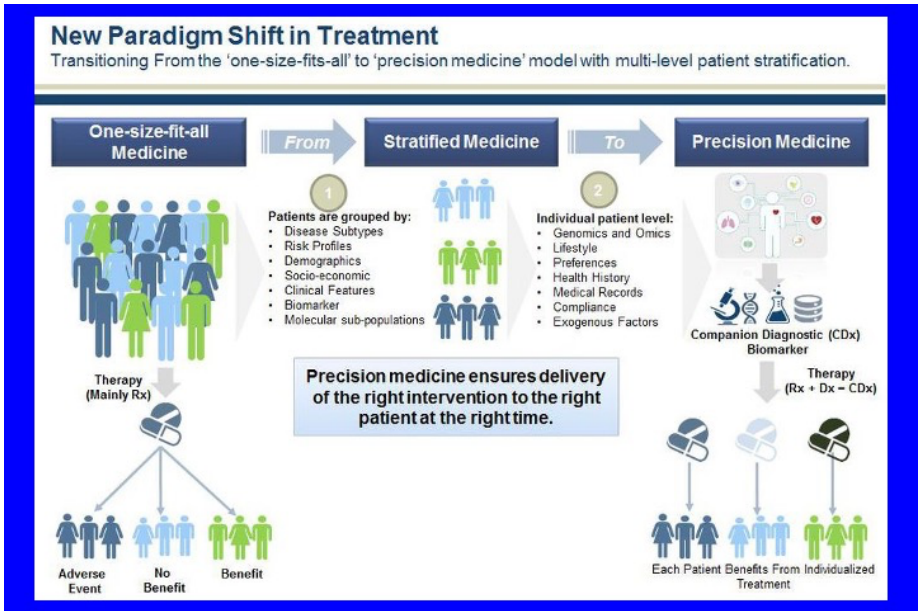


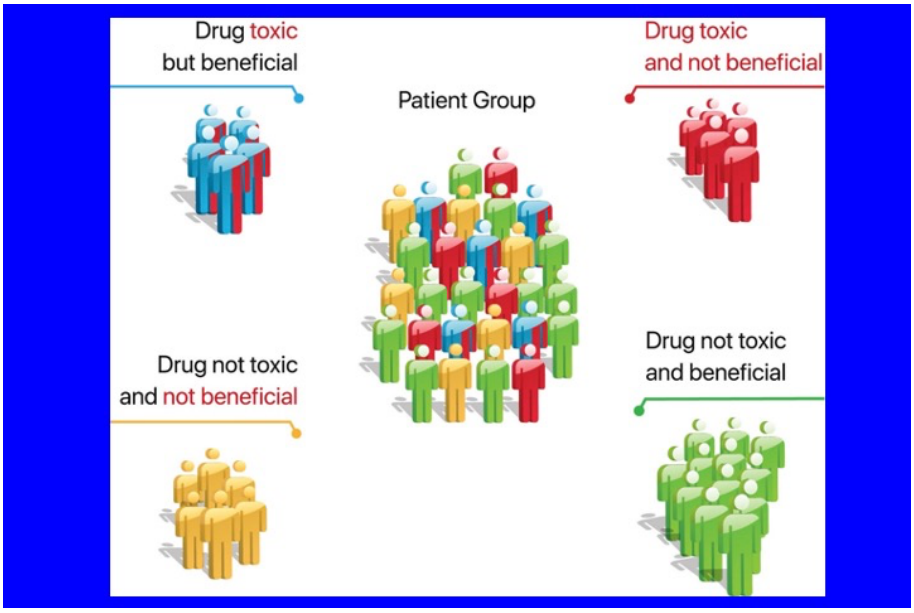
Regenerative Medicine: Definition

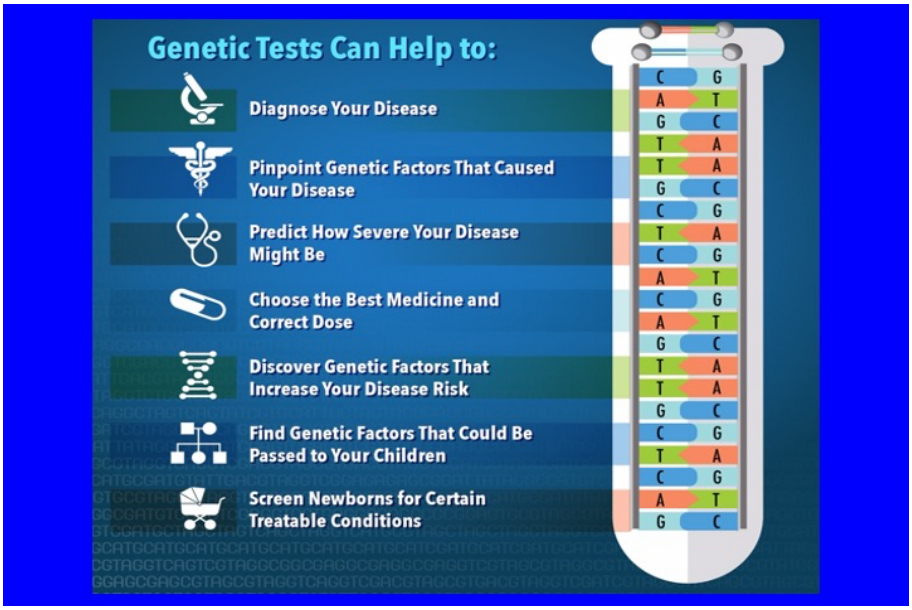
- 'Regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function.'[1] Includes different types of therapies. For instance[2]:
  - Stem cell therapy
  - Cellular therapy
  - Tissue engineering
  - Gene therapy (sits between stem cell and cellular therapy)
- Regenerative medicine has the potential to "deliver new, innovative therapies, or even **cures**, where conventional approaches do not provide adequate solutions[3]

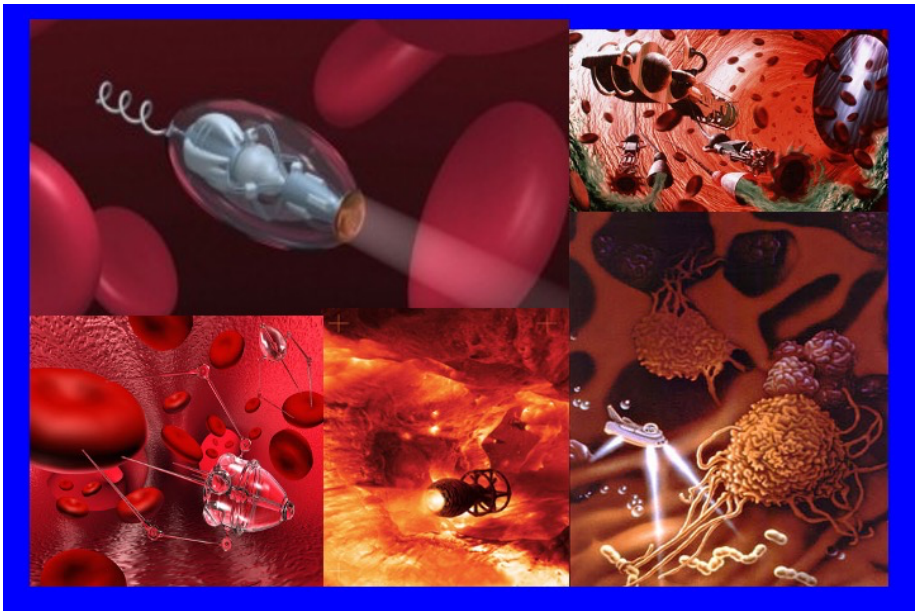

Regenerating a limb
A newt can regenerate an entire limb within 7-10 weeks.
Growth cycle
1 week
3-6 weeks
6-9 weeks

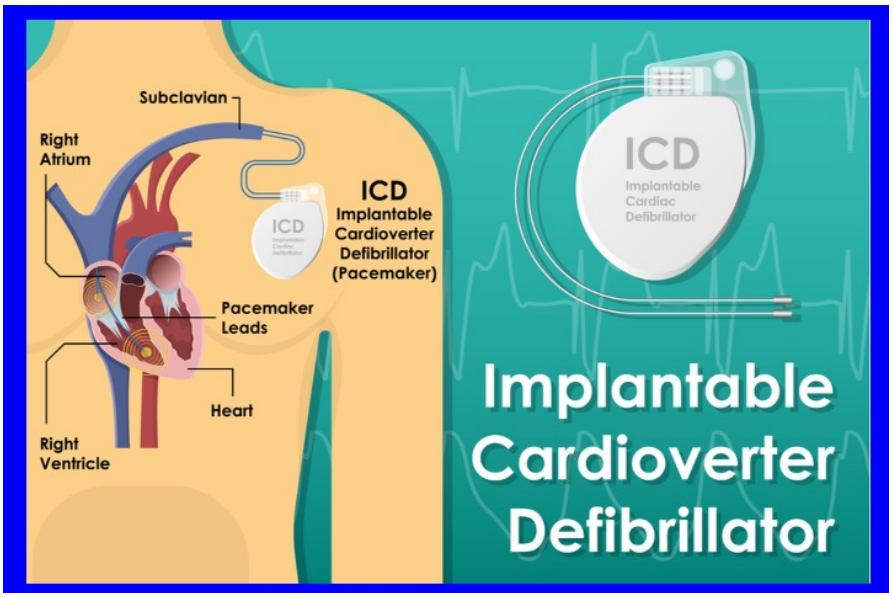

Planaria Regeneration
Planaria are flatworms (Platyhelminthes) and more complex than hydras. They have a remarkable regenerative ability. When a planaria is cut in two, each fragment will regenerate a complete animal. In fact, a single planaria can be cut into dozens of small pieces, and each can regenerate a complete new animal. This amazing ability seems to be related to the relative abundance of stem cells called neoblasts.

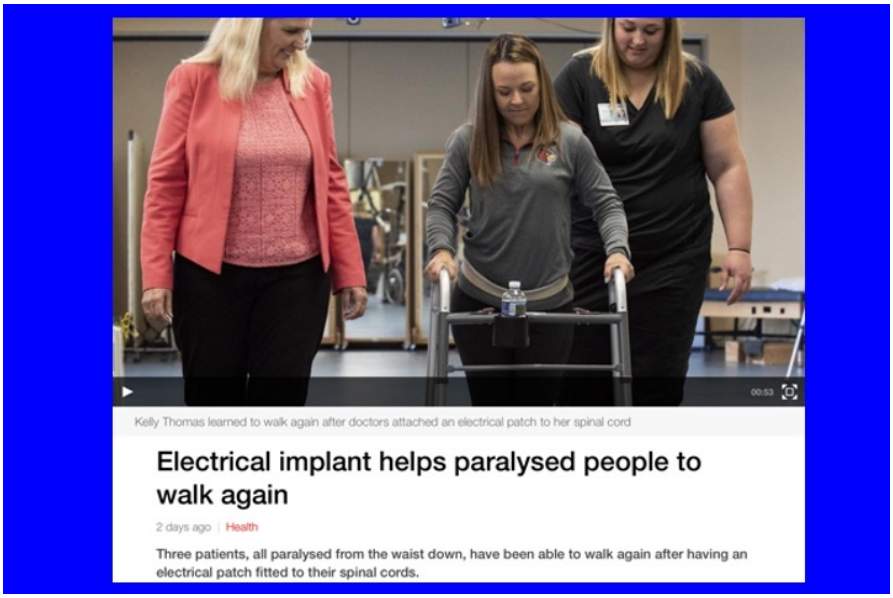

New Paradigm Shift in Treatment
Transitioning From the 'one-size-fits-all' to 'precision medicine' model with multi-level patient stratification.
One-size-fit-all Medicine
From
Stratified Medicine
To
Precision Medicine
1
Patients are grouped by:
Disease Subtypes
Risk Profiles
Demographics
Socio-economic
Clinical Features
Biomarker
Molecular sub-populations
2
Individual patient level:
Genomics and Omics
Lifestyle
Preferences
Health History
Medical Records
Compliance
Exogenous Factors
Companion Diagnostic (CDx) Biomarker
Therapy (Mainly Rx)
Therapy (Rx + Dx = CDx)
Precision medicine ensures delivery of the right intervention to the right patient at the right time.
Adverse Event
No Benefit
Benefit
Each Patient Benefits From Individualized Treatment


Drug toxic
but beneficial
Patient Group
Drug toxic
and not beneficial
Drug not toxic
and not beneficial
Drug not toxic
and beneficial


Genetic Tests Can Help to:
Diagnose Your Disease
Pinpoint Genetic Factors That Caused Your Disease
Predict How Severe Your Disease Might Be
Choose the Best Medicine and Correct Dose
Discover Genetic Factors That Increase Your Disease Risk
Find Genetic Factors That Could Be Passed to Your Children
Screen Newborns for Certain Treatable Conditions





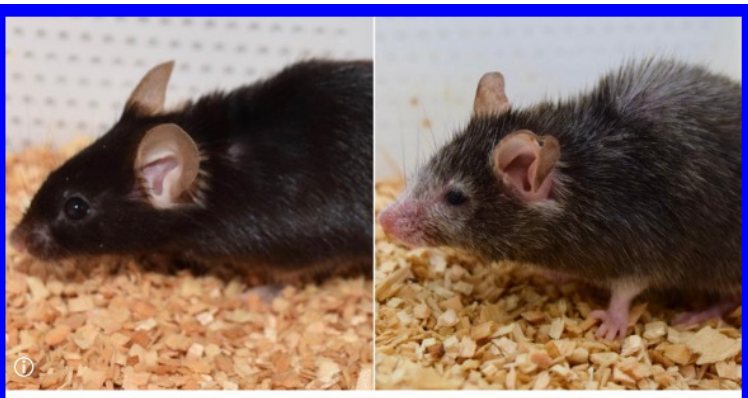


Kelly Thomas learned to walk again after doctors attached an electrical patch to her spinal cord

Electrical implant helps paralysed people to walk again

2 days ago | Health

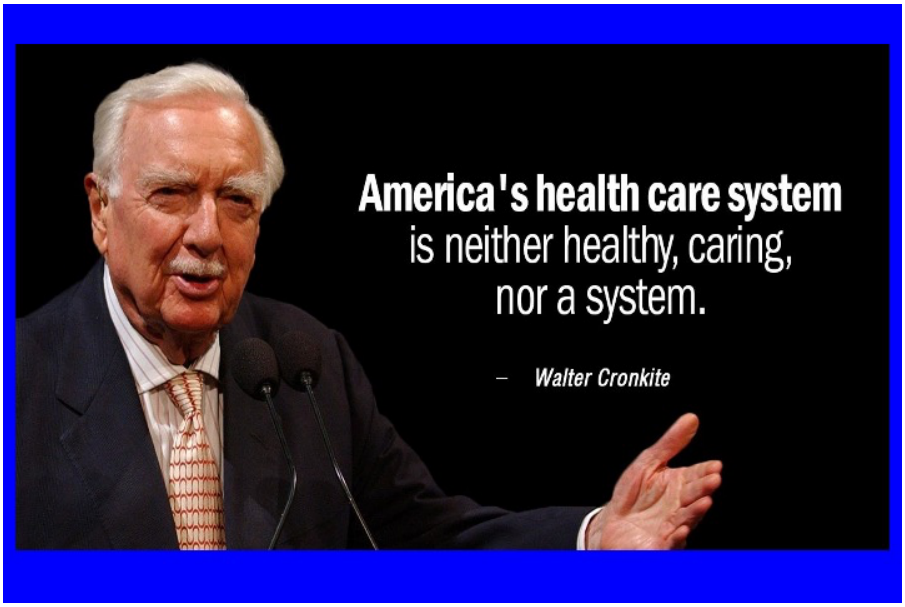
Three patients, all paralysed from the waist down, have been able to walk again after having an electrical patch fitted to their spinal cords.



The 'Benjamin Button' effect: Scientists can reverse aging in mice. The goal is to do the same for humans

By Sandee LaMotte, CNN

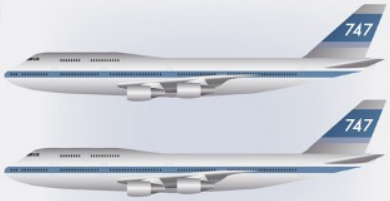
Updated 3:22 PM ET, Fri July 15, 2022



440,000

US deaths **PER YEAR** from **PREVENTABLE** medical errors

1,000 PEOPLE EVERY DAY



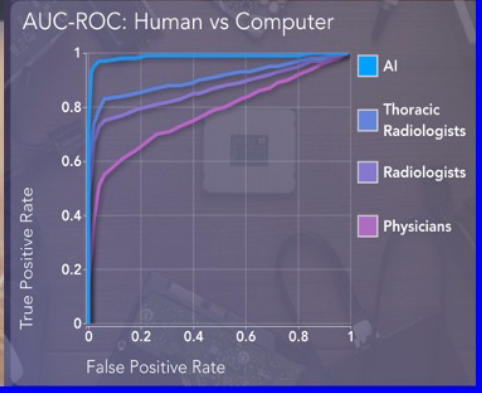
= **2** 747 JUMBO JETS

Artificial Intelligence can reduce medical errors, enhance diagnostic & therapeutic accuracy

AI Outperforms Dermatologists in Diagnosing Skin Cancer

AI vs Doctors: Chest X-Rays

AI was significantly more accurate and precise than radiologists and physicians in diagnosing chest x-rays.



Tips for Living Younger Longer

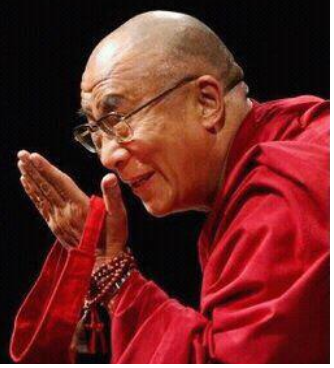
- Exercise body & mind, flexibility, and balance
- Mediterranean pesco-vegetarian diet, antioxidants
- Ideal body weight, intermittent fasting
- Preventive, personalized, precision health care
- Proactive stress reduction, enhance immunity
- Social activity with friends and family
- Meditation, practice of belief
- Reduce tobacco, alcohol, sitting is the new smoking
- Enjoy and experience all of your senses including purpose, empathy, gratitude, humor, and common sense

The secret to living well and longer is:

"Eat half, walk double, laugh triple,
and love without measure."

Tibetan Proverb

The Dalai Lama, when asked what surprised him most about humanity, answered "Man. Because he sacrifices his health in order to make money. Then he sacrifices money to recuperate his health. And then he is so anxious about the future that he does not enjoy the present; the result being that he does not live in the present or the future; he lives as if he is never going to die, and then dies having never really lived."



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CME Questions

1. Longevity research efforts include which of the following areas of inquiry?

   A. Caloric restriction
   B. Exercise
   C. Pharmaceuticals
   D. Stem cells
   E. All of the above*

2. Human longevity may be enhanced by advances in biotechnology and nanotechnology.

   A. True*
   B. False

3. Life span is synonymous with health span.

   A. True
   B. False*

4. Factors in aging include:

   A. Glycation
   B. Cellular autophagy
   C. Oxidative stress
   D. Telomere shortening
   E. All of the above*

5. Benefits of intermittent fasting include:

   A. Increase in cellular autophagy
   B. Stimulation of brain function
   C. Enhancement of immune system
   D. Improved cardiovascular function
   E. All of the above*

6. Human health and longevity may be improved with increasing adoption of which of the following?

   A. Precision medicine
   B. Personalized medicine
   C. Artificial intelligence
   D. Enhanced safety efforts to avoid medical errors
   E. All of the above*

7. While human lifespan is currently limited, there are remarkable examples of regenerative capacity, longevity, and even immortality that are being actively investigated by science.

   A. True*
   B. False